IN THE UNITED STATES DISTRICT COURT
DISTRICT OF UTAH, CENTRAL DIVISION

IN RE: BRCA1- AND BRCA2- BASED HEREDITARY CANCER TEST PATENT LITIGATION THIS DOCUMENT RELATES TO: UNIVERSITY OF UTAH RESEARCH FOUNDATION, *et al*. Plaintiffs, vs. AMBRY GENETICS CORPORATION, Defendant.	MDL CASE NO. 2:14-MD-2510 CASE NO. 2:13-CV-00640-RJS **MEMORANDUM DECISION AND ORDER DENYING PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION** Judge Robert J. Shelby

On June 13, 2013, the Supreme Court issued a unanimous decision holding that "genes and the information they encode are not patent eligible simply because they have been isolated from the surrounding genetic material." *Association for Molecular Pathology v. Myriad Genetics Corp.* (*AMP*), 133 S. Ct. 2107, 2120 (2013). This case arises in the aftermath of that decision.

Plaintiff Myriad Genetics, Inc. (Myriad) is recognized as the winner in the "race" to locate and sequence the BRCA1 and BRCA2 genes.[1] Myriad invested millions of dollars, including money obtained via public grants, in an effort to locate and sequence those genes in the early-to-mid-1990s. Once it did, Myriad sought and obtained related patents, some of which will begin to expire in August 2014. Myriad also developed and commercialized tests to screen people for the presence of harmful variations in these genes. Myriad launched its flagship 'BRACAnalysis' test in 1996 and debuted its 'myRisk' test in 2013. Ford Decl. at ¶¶ 1-3, 8

[1] *See Fierce Competition Marked Fervid Race For Cancer Gene*, Natalie Angier, New York Times, Sept. 20, 1994, <http://www.nytimes.com/1994/09/20/science/fierce-competition-marked-fervid-race-for-cancer-gene.html?pagewanted=all&src=pm>.

(Dkt. 6).[2] Between 1997 and 2013, Myriad's revenue from its BRACAnalysis test steadily increased, and now totals more than $2 billion. Kearl Decl. at 6 (Dkt. 107). Myriad earned that revenue by carefully guarding its patent rights and preventing others from providing screening tests for the BRCA1 and BRCA2 genes. From the mid-1990s, until the Supreme Court's *AMP* decision, Myriad was the lone provider of full-sequence BRCA1 and BRCA2 tests in the United States. Ford Decl. at ¶ 8.

Within days of the Supreme Court's *AMP* decision, Defendant Ambry Genetics Corporation (Defendant) announced plans to sell tests less expensive than Myriad's to screen BRCA1 and BRCA2 genes. Since then, other companies have followed suit—publicly offering such tests or announcing plans to do so.[3]

Soon after Defendant announced it would begin to offer BRCA1 and BRCA2 testing, Plaintiffs filed this action, complaining that Defendant's genetic testing infringes several of

[2] Unless otherwise noted, citations to the parties' case filings will refer to materials filed in Case No. 2:13-CV-00640, the first filed of Plaintiffs' cases in this court.

[3] These companies include Gene by Gene, Ltd.; Counsyl, Inc. (Counsyl); Quest Diagnostics (Quest); GeneDx; Invitae Corporation (Invitae); and Laboratory Corporation of America Holdings (LCAH). Since the filing of the Motion for Preliminary Injunction against Defendant, Plaintiffs, including Myriad, have sued Gene by Gene, Quest, GeneDx, Invitae, and LCAH in this court. *See* Case Nos. 2:13-CV-00643 (dismissed without prejudice on Feb. 7, 2014); 2:13-CV-00967; 2:13-CV-00954; 2:13-CV-01049; and 2:13-CV-01069, respectively. Myriad was also sued in the Northern District of California by Counsyl (Case No. CV-13-04391-NC) and Invitae (Case No. 13-05495) and in the Central District of California by Quest (Case No. 8:13-CV-01587-AG-DFMx). Myriad subsequently moved the Judicial Panel on Multidistrict Litigation to transfer these California cases to the District of Utah. (MDL No. 2510.) That Panel granted Myriad's request, and the California actions have been transferred to this court as part of Case No. 2:14-MD-2510, joining this case and the cases that Plaintiffs have filed against GeneDx and Quest. Plaintiffs have not moved for injunctions against Quest, GeneDx, Invitae, or LCAH. Plaintiffs and Gene by Gene recently stipulated to dismissal without prejudice of Plaintiffs' claims and Gene by Gene's counterclaims. (Dkt Nos. 90 and 91 in Case No. 2:13-CV-00643.)

Plaintiffs' patents.[4] Plaintiffs now move the court for a preliminary injunction enjoining Defendant's sales or offers to sell "genetic tests including a BRCA1 or BRCA2 panel" pending trial on the merits.[5] Plaintiffs' Motion focuses on ten claims in the patents-in-suit: 1) four claims to pairs of synthetic DNA strands, called "primers"; and 2) six methods claims for analyzing BRCA1 and BRCA2 sequences. Plaintiffs argue these claims remain patent eligible after the *AMP* litigation, and that Defendant's testing infringes the patents containing these claims. Plaintiffs contend an injunction is necessary to prevent irreparable harm to their pricing structure, share of the BRCA1 and BRCA2 testing market, corporate reputation, and other exclusive benefits they might enjoy during the remainder of their patents' terms.

Defendant opposes Plaintiffs' Motion, arguing that Plaintiffs cannot show that they are likely to succeed on the merits of their infringement claims because Defendant has raised a "substantial question" concerning the subject matter eligibility of Myriad's BRCA1 and BRCA2-related patents, particularly in light of the recent *AMP* litigation. Defendant further contends there are substantial questions concerning whether: 1) its testing infringes Plaintiffs' patent claims; 2) the patents at issue are invalid because the inventions they claim were anticipated and

[4] Plaintiffs allege Defendant is infringing: claim 6 of U.S. Patent No. 5,709,999 (the '999 Patent); claims 6, 16, and 17 of U.S. Patent No. 5,747,282 (the '282 Patent); claims 7, 8, 12, 23 and 26 of U.S. Patent No. 5,753,441 (the '441 Patent); claims 29 and 30 of U.S. Patent No. 5,837,492 (the '492 Patent); claim 4 of U.S. Patent No. 6,033,857 (the '857 Patent); claims 2, 3, and 4 of U.S. Patent No. 5,654,155 (the '155 Patent); claims 2, 3, 4, 5, 6, and 7 of U.S. Patent No. 5,750,400 (the '400 Patent); claims 32 and 33 of U.S. Patent No. 6,051,379 (the '379 Patent); claim 5 of U.S. Patent No. 6,951,721 (the '721 Patent); claims 3, 4, 5, 6, 7, 8, 11, 14, 17, 18, and 19 of U.S. Patent No. 7,250,497 (the '497 Patent); claims 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, and 18 of U.S. Patent No. 7,470,510 (the '510 Patent); claims 10, 11, 15, 16, 17, and 19 of U.S. Patent No. 7,622,258 (the '258 Patent); claims 2, 8, and 16 of U.S. Patent No. 7,838,237 (the '237 Patent); claims 2, 3, 5, 9, 10, and 12 of U.S. Patent No. 7,670,776 (the '776 Patent); and claims 2 and 7 of U.S. Patent No. 7,563,571 (the '571 Patent). Am. Compl. (Dkt. 21).

[5] Plaintiffs' Proposed Order (Dkt. Nos. 5 and 5-1.)

obvious; and 3) the patents are invalid due to indefiniteness or lack of written description. Defendant also argues that Plaintiffs will suffer no immediate, irreparable harm to their pricing, market share, or reputation. Finally, Defendant asserts that its business will be devastated and the public interest harmed if an injunction issues because the public would lose access to less expensive, more complete, and more innovative cancer testing.

On September 11 and 12, and October 7, 2013, the court received testimony and argument on Plaintiffs' Motion. Additionally, the parties have submitted numerous declarations from experts. Having carefully considered the relevant authorities, briefing from the parties and amici, oral argument, testimony, and the evidence, the court concludes Plaintiffs are not entitled to a preliminary injunction. The court finds that although Plaintiffs have shown they are likely to be irreparably harmed if an injunction does not issue, Defendant has raised substantial questions concerning whether any of the patent claims at issue in Plaintiffs' Motion are directed toward patent eligible subject matter under 35 U.S.C. § 101. In light of Defendant's showing, Plaintiffs are unable to establish that they are likely to succeed on the merits of their claims. Neither have Plaintiffs established that the equitable factors support issuance of the requested injunction. Having failed to satisfy their burden, Plaintiffs' Motion for Preliminary Injunction must be denied.

I. FACTUAL BACKGROUND

A. The Parties

1. Plaintiffs

Myriad is a Delaware molecular diagnostic corporation with its principal office in Salt Lake City, Utah. The University of Utah is a Utah nonprofit educational and research institution in Salt Lake City. The University of Pennsylvania is a Pennsylvania nonprofit educational and

research institution in Philadelphia. The Hospital for Sick Children is a pediatric heath care and research facility located in Toronto, Ontario. Endorecherche is a Canadian medical research corporation in Ste-Foy, Quebec. Myriad owns the following patents-in-suit: the '155, '400, '379, '721, '497, '510, '258, '237, '776, and '571 Patents. *See supra* note 4 (listing complete numbers for patents-in-suit). Myriad is the exclusive licensee of the '999, '282, '441, '492, and '857 Patents. The University of Utah is the owner or co-owner of three patents at issue in this case, the '999, '282, and '441 Patents. The University of Utah, University of Pennsylvania, the Hospital for Sick Children, and Endorecherche are the co-owners of the '857 and '492 Patents. The University of Utah Research Foundation, also a Plaintiff, has received from Myriad over $40 million in royalties under some of the patents at issue in this case over the past two decades. Pershing Decl. at ¶ 4 (Dkt. 112).

2. Defendant

Defendant is a clinical diagnostic and genomic services company in Aliso Viejo, California. In the hours after the Supreme Court issued its *AMP* decision, Defendant announced that it would begin offering a number of its own tests that include BRCA1 and BRCA2 screening. Defendant now offers a menu of at least six tests that include screening for BRCA1 and BRCA2: a combined BRCA1/BRCA2 test, BRCAPlus, BreastNext, PancNext, Ova Next, and CancerNext. Chao Decl. at ¶ 16, Exhs. B-G (Dkt. 56). Defendant's BRCA1/BRCA2 test is available for $2,200—substantially less than the price for comparable testing offered by Myriad. *Id.*

3. Amici

The court permitted the filing of a joint Amicus Curiae brief in support of Defendant's Opposition to Plaintiffs' Motion for Preliminary Injunction. (Dkt. 79.) Amici are the American

Civil Liberties Union (ACLU) and ACLU of Utah Foundation, Inc. (ACLU Utah), Public Patent Foundation (PUBPAT), Association for Molecular Pathology (AMP), Breast Cancer Action (BCAction), and the AARP. The ACLU and PUBPAT represented the individual and organizational plaintiffs in the *AMP* litigation, including two of the amici here, *AMP* and BCAction. AARP also filed amicus briefs in the *AMP* litigation.

The ACLU describes itself as a "nationwide, nonprofit, nonpartisan organization with over 500,000 members" with the stated goal of protecting rights protected under the Constitution. *Id.* at 4. ACLU Utah is a regional affiliate of the ACLU. *Id.* PUBPAT is a not-for-profit legal services organization affiliated with the Benjamin N. Cardozo School of Law and is concerned with patent policy issues. *Id.* at 4-5. *AMP* is "an international not-for-profit professional association representing over 2,000 physicians, doctoral scientists and medical technologists who perform laboratory testing based on knowledge derived from molecular biology, genetics and genomics." *Id.* at 5. *AMP* claims an interest in this matter because, in its view, the issues in this case will impact "the provision of and innovation in genetic testing." *Id.* BCAction is "a national, grassroots advocacy and education organization" working to end breast cancer. It holds itself out as "the watchdog of the breast cancer movement." *Id.* AARP is a "nonpartisan, nonprofit organization with a membership dedicated to addressing the needs and interests of people age fifty and older," seeking to "enhance the quality of life for all by promoting independence, dignity, and purpose." *Id.* at 6. AARP's mission is focused, in part, on healthcare-related issues. *Id.*

B. Background on Genetics

Plaintiffs and Defendant generally do not dispute the core scientific principles underlying the genetics issues in this case. Here, the court relies upon expert declarations and testimony submitted by Plaintiffs and Defendant.

1. DNA

Genes are the units responsible for inheritance of discrete traits, such as the color of peas in a peapod. Kay Decl. at ¶ 15 (Dkt. 103); Tait Decl. at ¶ 32 (Dkt. 54). Genes are made from segments of deoxyribonucleic acid, or DNA. DNA is an integral component of chromosomes, the complex structures that carry genes and which are located within most cells of the human body. Pribnow Decl. at ¶ 18 (Dkt. 65); Kay Decl. from *AMP* Litigation at ¶ 131 (Dkt. 34-4). The human genome, the "whole of the genetic information of an organism," is comprised of about 22,000 genes residing in 23 pairs of chromosomes. Tait Decl. at ¶ 32. Every cell in the human body contains a complete copy of the human's genome.

DNA is a chemical compound containing within its molecular structure the genetic information necessary to code for most, if not all, aspects of embryogenesis, development, growth, metabolism, and reproduction. Pribnow Decl. at ¶ 22. At its most basic level, a DNA molecule is composed of five chemical elements: carbon, hydrogen, oxygen, nitrogen, and phosphorus. Kay Decl. at ¶ 12.

But DNA is unique from other molecules in that it encodes—provides the blueprint for—our highly organized, intricate, complex internal structures, and serves as the template for the complex molecules that allow us to extract, transform, and utilize the energy that is present in our environment. It can be said that DNA contains information necessary for all life functions. Aug. 23, 2013 Tutorial (Jackson) at 8:3-10, 8:22–9:18 (Dkt. 117); Nussbaum Decl. at ¶¶ 41-65

(Dkt. 61); Pribnow Decl. at ¶ 33; Pribnow 2nd Decl. at ¶¶ 21-24 (Dkt. 132). It is DNA's unique, informational aspect that sets it apart from other biological molecules. Tait Decl. at ¶ 32.[6]

The information in DNA is stored in the sequence of adjacent bases within the DNA strand through what is termed a "nucleotide sequence." Scientists often refer to DNA as a "polynucleotide," reflecting that DNA consists of a contiguous chain of chemical units called "deoxyribonucleotides." Pribnow Decl. at ¶¶ 22-23. The standard nucleotides in vertebrate DNA contain four different bases: adenine, thymine, cytosine, and guanine. As shorthand, scientists often denote nucleotides by the first letter of the names of their bases: "A" for adenine; "G" for guanine; "T" for thymine; and "C" for cytosine. These bases are linked together by chemical bonds via a sugar-phosphate backbone. Kay Decl. at ¶ 12. A DNA molecule is typically represented by the linear order of the nucleotide sequence.

Scientists can extract DNA from cells in the body. Such DNA is known as extracted "genomic" DNA or gDNA. Scientists can also chemically synthesize DNA. Whether genomic or synthetic, all DNA uses the same four nucleotides, and the information encoded in a specific nucleotide sequence is the same. Pribnow Decl. at ¶¶ 19-21, 27, 52-54; Pribnow 2nd Decl. at ¶¶ 5-11.

DNA often exists as a double helix, with two intertwined strands. This structure is made possible because each base in one strand is paired via hydrogen bonds with another base in the

[6] In their Reply Brief, Plaintiffs dispute that DNA contains information, stating that "DNA and any segment of DNA do not contain 'information' (like computer or computer storage device or any analogous device)." Pls.' Reply Br. at 4 (Dkt. 98 at 16). But at the court's September 11, 2013 hearing, Myriad's corporate representative, Vice President for Technology Development and Laboratory Director, Dr. Ben Roa, testified that he agreed with the statements that "DNA can contain information," and that specifically "BRCA1 and BRCA2 genes do provide information relating to a patient's susceptibility to developing breast or ovarian cancer . . . ." Sept. 11, 2013 Hearing Tr. (Roa) at 105:9-17 (Dkt. 150).

other, complementary strand. Kay Decl. at ¶ 14. To better understand DNA's role as an informational molecule, one must understand the rules of base pair complementarity, or "Watson-Crick" base pairing, named after two of the scientists credited with deducing the structure of DNA upon recognizing the critical importance of base pair complementarity. Pribnow Decl. at ¶ 28. In Watson-Crick pairing, A pairs exclusively with T, while C pairs only with G. *Id*. at ¶¶ 28-29. The informational aspects of DNA are based on associations between the nucleotides that are governed by the natural law of Watson-Crick base pairing. Nussbaum Decl. at ¶¶ 41-65; Pls.' Reply Br. at 5 (Dkt. 98); Pribnow Decl. at ¶¶ 28-50.

A single-stranded DNA molecule has "directionality," meaning that the two ends of the molecule are chemically different. The "beginning" of a DNA molecule is called the 5' (5 prime)-end and the "end" of the molecule is called the 3' (3 prime)-end. Kay Decl. at ¶ 17. DNA also contains regions that can code for protein molecules. Protein-coding segments of native DNA are contained in "exons." *Id.* at ¶ 18. In humans, protein-coding exonic DNA sequences are typically interrupted by intervening DNA sequences known as "introns" that do not code for proteins, but may contain regulatory elements—which control when a cell activates a gene. *Id.*

DNA replicates through a complex process. Pribnow Decl. at ¶ 36. During replication, the DNA double helix is "unwound" and separated into single strands. *Id.* Single-stranded DNA binding proteins maintain DNA in its single-stranded conformation, preventing the strands from reassociating through Watson-Crick base pairing. Pribnow 2nd Decl. at ¶¶ 30-32. The two single strands of DNA then become templates for the synthesis of the strand that will form the opposite strand in a new double helix. Pribnow Decl. at ¶¶ 36-38; Pribnow 2nd Decl. at ¶¶ 13-17. DNA replication is "primed" by the presence of a short RNA primer that the enzyme responsible for

synthesizing new DNA – "DNA polymerase" – uses as a starting point to synthesize the new DNA strand. Pribnow 2nd Decl. at ¶¶ 13-17. The opposite strands are synthesized according to Watson-Crick base pairing rules, resulting in two identical copies of the original DNA sequence. *Id.* The entire genomic DNA of all human cells—all forty-six chromosomes' worth (in twenty-three chromosome pairs)—is completely copied from end to end during each replication cycle. Pribnow Decl. at ¶ 37. Thus, all base pairs comprising the genome are exposed in an extended single-stranded form during each replication event. *Id.* In humans, this occurs trillions of times during the life of every person. *Id.* Both the integrity of the structure and the nucleotide sequence of each single strand of the entire double helix are critical for maintaining the fidelity of replication during the vast number of cell division events that occur. *Id.*

A change in the gene sequence is called a genetic "variant" or "polymorphism." Any change, even to a single nucleotide, can constitute a variant. Some variants are harmless. Others, termed "mutations," can cause disease or increase the risk of disease. Disease conditions in humans frequently are due to mutations in an individual's copy of a single gene that gives rise to a protein different from the normal, or "wild-type," protein expressed in persons without the disease. The genetic mutation that is responsible for such protein alteration may be determined and may be observed relatively easily through analysis of a person's DNA sequence from a human sample. Tait Decl. at ¶ 34. These mutations can be found in exons or introns, although it is often easier for geneticists to identify disease-causing mutations in exons. Hence, mutation screens often concentrate on examining DNA sequences containing exons. Kay Decl. at ¶ 19.

In some instances, there is not enough information about a variant to classify it—the variant's effect on the body is currently unknown. Such a variant is termed a "variant of unknown significance," or "VUS." The significance of the variant may be determined over time

though the collection and analysis of more data for that variant. Swisher Decl. at ¶ 40 (Dkt. 59); Nussbaum Decl. at ¶¶ 66-68. Through further investigation, most VUS results are ultimately reclassified as either deleterious or benign. The vast majority are reclassified as benign. Of course, the number of VUS reported is inversely proportional to the completeness of a genetic database. The more mutations discovered and characterized, the fewer VUS results will be returned. Nussbaum Decl. at ¶¶ 66-67.

2. RNA

RNA, or ribonucleic acid, is a chemical compound with four bases: guanine, cytosine, uracil, and adenine. Kay Decl. at ¶ 20. Thus, instead of DNA's thymine base, RNA contains uracil. *Id.* Common abbreviations of the RNA bases are: "G" for guanine, "C" for cytosine, "U" for uracil, and "A" for adenine. *Id.* Each base, together with one sugar and one phosphate molecule, makes up one repeating unit known as an RNA nucleotide. *Id.* Also like DNA, RNA is formed by a strand of bases that are linked together via a sugar-phosphate backbone. *Id.* The structures of the sugar-phosphate backbone of RNA and DNA, however, are different; while RNA contains a ribose sugar, the sugar component of DNA is a deoxyribose. *Id.* Because of these differences in structure, RNA usually exists as a single strand instead of the double helix associated with DNA. *Id.* DNA is generally more stable than RNA. *Id.*

RNA is generated in the body from DNA in a process called "transcription." *Id.* at ¶ 21. During transcription of RNA from DNA, a discrete segment of the DNA unwinds, and the bases of the DNA molecule act as "clamps" that hold the bases of the newly forming RNA in place while the chemical bonds of the sugar-phosphate backbone are formed. *Id.* This process is mediated by a structure in the cell known as RNA polymerase. *Id.*

A newly transcribed RNA molecule (transcript), or precursor messenger RNA (pre-mRNA), is processed to result in a mature messenger RNA (mRNA). *Id*. at ¶ 22. Pre-mRNA contains nucleotides that are eliminated during a process called "splicing." *Id.* This involves splicing the introns out of the pre-mRNA, while the exons are ligated, or joined together, to form the intact mRNA molecule. *Id.*

3. Proteins

Proteins are generally large, complex molecules that play many critical roles in the body. *Id*. at ¶ 23. They are required for the structure, function, and regulation of the body's tissues and organs. *Id.* Proteins are made up of hundreds or thousands of smaller units called amino acids, which are attached to one another in long chains. *Id.* There are 20 different amino acids that can be combined to make a protein. *Id.* The sequence of amino acids determines each protein's unique 3-dimensional structure and its specific function. *Id.* Proteins are translated from mRNA through a process called "translation." *Id.* at ¶ 24. During translation, mRNA serves as a template to assemble a protein. *Id.* Three consecutive bases in an mRNA molecule constitute a "codon," which codes for one of the twenty amino acids. *Id.* Pairing interactions take place between an mRNA molecule and another RNA molecule known as tRNA, which serves as an adaptor during protein translation. *Id.* Specifically, sets of three nucleotides in the coding region of an mRNA react with three nucleotides in a tRNA in such a way as to cause the amino acid linked to the tRNA molecule to be chemically transferred to the growing polypeptide (a chain of amino acids linked together by peptide bonds) destined to become a protein. *Id.* The bases of the mRNA serve as "clamps" to hold the amino acids in place while the chemical bonds between the individual amino acids are formed. During translation, the mRNA template, the tRNA, the newly-forming polypeptide chain, and the next amino acid reside in a multi-protein complex

called a ribosome. *Id.* Once a protein is translated it typically undergoes post-translational or chemical modifications that are important for the protein's function. *Id.*

The genetic code describes which codons code for which amino acids. *Id.* at ¶ 25. For example, the codon adenine-thymine-guanine encodes the amino acid methionine. *Id.* Thus, the chemical composition of an mRNA molecule determines the amino acid composition of a protein. *Id.*

4. cDNA

Complementary DNA, or "cDNA," is commonly synthesized from a mature mRNA in a reaction catalyzed by a protein known as reverse transcriptase. *Id.* at ¶ 26. cDNA is so named because each base in the cDNA can bind to a base in the mRNA from which the cDNA is synthesized. *Id.* In other words, it is "complementary" to the mRNA from which it is synthesized. *Id.* cDNA can be structurally different from native DNA. Most notably, cDNA made from an mRNA does not contain introns. *Id*. at ¶ 27. DNA generally contains intronic sequences—although DNA fragments may contain only exons. cDNA is also functionally different from DNA. *Id*. at ¶ 28. Most critically, DNA contains regulatory sequences. *Id.* These regulatory sequences are not present in cDNA because they are not present in the mRNA from which the cDNA is synthesized. *Id.*

5. Primers and Probes

A primer is a short, synthetic, single-stranded DNA molecule that binds specifically to an intended target nucleotide sequence. *Id.* at ¶ 29. The sequence of the primer is necessarily complementary to the target sequence, so that the bases of the primer and the bases of the target sequence bind to each other. *Id.* In human genetic testing, primers bind to human gene sequences that are an exact match according to the law of Watson-Crick base pairing. Pribnow

Decl. at ¶ 91. Binding a primer to its target sequence is the first step in amplifying a segment of DNA—the production of multiple copies of a specific DNA segment for DNA sequencing reactions or other molecular characterization. *Id.*; Kay Decl. at ¶¶ 29-30.

Scientists create primers. In so doing, they consider primer size and other aspects, such as the exact portion of the DNA segment targeted. Pribnow 2nd Decl. at ¶ 8. These considerations are dictated by the nucleotide sequence of the DNA segment to which the primer is intended to bind. *Id.* For example, if the targeted sequence is a naturally occurring BRCA1 or BRCA2 sequence, the starting points for primer creation necessarily must be the complement of the naturally occurring BRCA1 or BRCA2 sequences flanking the specific DNA region the scientist wishes to amplify. *Id.* Because the primers in a pair are designed to "hybridize" to their BRCA primer binding sites per Watson-Crick base pairing rules, the BRCA primers must contain sequences identical to the BRCA sequence directly opposite its binding sites. *Id.*

Typical primer pairs used in the most common method of DNA amplification, polymerase chain reaction (*see* discussion of polymerase chain reaction *infra* Part I.B.6.), are between 15 to 18 nucleotides or 25 to 30 nucleotides in length. Roa Decl. at ¶ 16 (Dkt. 63); Pribnow Decl. at ¶ 91. To hybridize well to a person's DNA, the length of the nucleotide sequence of the primer that binds to the sample DNA should be at least 15 nucleotides long. Roa Decl. at ¶¶ 16, 21-22.

In addition to sequences that are identical to naturally occurring DNA sequences, primers may have additional appended sequences on their ends, such as "Next Generation Sequencing (NGS) adaptor sequences." These adaptor sequences do not hybridize to the targeted genetic sequence. Elliott Decl. ¶¶ 15-17 (Dkt. 47); Elliott 2nd Decl. at ¶¶ 4-5 (Dkt.

136). Neither do they affect a primer pair's function in hybridizing to portions of a targeted DNA sequence. The primer pairs bind to and prime the same portion of the DNA sequence regardless of the presence or makeup of any such appended molecule. Elliott Decl. at ¶¶ 15-17; Elliott 2nd Decl. at ¶¶ 4-5.

Genetic testing methods can also utilize "probes." Pribnow Decl. at ¶ 85. Probes are similar to primers in that they are short segments of DNA that are capable of hybridizing to a DNA segment according to the rules of Watson-Crick base pairing. *Id.* A probe is used to detect the presence or absence of a particular DNA sequence in a DNA sample. Tait Decl. at ¶ 26. Thus, as with primers, the composition of a probe is dictated by the DNA sequence a scientist wants to identify. *Id*. at ¶ 24. The probe's DNA sequence is a complement to the sequence of DNA the probe will be used to detect, so that the probe will hybridize to the DNA target through Watson-Crick base pairing. Pribnow Decl. at ¶¶ 85-87; Tait Decl. at ¶¶ 22-26.

Primers and probes may utilize sequences that can hybridize to the sequence that would be present in a cDNA of the gene. In other words, primers and probes can hybridize to exonic-only sequences. But, primers and probes are not cDNA. Pribnow Decl. at ¶ 86. cDNA is typically not used as a primer or probe. *Id*. at ¶ 84. In the genetic testing that Plaintiffs contend their patent claims cover, cDNA may not be used much at all. *Id.* Rather, one simply amplifies a segment of DNA and uses it to interrogate a gene for medically important mutations. *Id.* cDNA is not typically used as a probe or primer in genetic testing in part because it is too large. *Id.* In addition, primers often are designed to hybridize to noncoding regions of the gene (introns) in order to copy the sequence of the intron immediately adjacent to the exon, in addition to the exon itself, thus mirroring the native nucleotide sequence. *Id.* Since cDNA does not contain introns, it cannot be used as a primer in this application. *Id.* Genomic DNA extracted

from the body is not typically used as primers or probes, although it would be possible to do so. *Id.* at ¶ 88.

Using probes and primers in genetic testing, including BRCA testing, does not fundamentally change the DNA that is analyzed. Pribnow Decl. at ¶ 87. More specifically, primers and probes do not alter the underlying, naturally occurring DNA sequence that is being read. *Id.* Therefore, they do not alter the underlying DNA's functional properties or identity for the purposes of genetic testing. *Id.*

At the time of Myriad's patents, the techniques for creating primers were well known in the art. Primers were generally created using commercially available "oligonucleotide synthesizing machines." *See* '282 Patent col.16 ll.43-48 (BRCA1); '492 Patent col.15 ll.30-37 (BRCA2).

As with primers, the creation and use of DNA probes in genetic testing experiments was well known and widely used prior to August 1994, when Myriad submitted its application for the first of the patents at issue in Plaintiffs' Motion. Tait Decl. at ¶ 26; '282 Patent col.15 ll.9-20, col.17 ll.15-32, col.21 ll.34—col.22 l.25. Probe hybridization results from Watson-Crick base pairing between two complementary strands of nucleic acids. Hybridization, a form of binding between molecules, occurs as a result of the inherent chemical properties of nucleic acid molecules and gives double-stranded DNA its characteristic helical structure. Tait Decl. at ¶ 22.

6. Polymerase Chain Reaction

Many copies of an input DNA are required to sequence genes. Those who want to sequence and test human genes utilize methods for amplifying—creating copies—of a segment of genomic DNA products. Kay Decl. at ¶ 31; Pribnow Decl. at ¶ 17. Whether produced in a laboratory or by nature, amplified DNA is indistinguishable from the original DNA that was

copied, both in its chemical structure and, importantly, the sequence information contained in the DNA. Pribnow Decl. at ¶ 19.

The most widely used DNA amplification method is the polymerase chain reaction (PCR). Kay Decl. at ¶ 32. PCR mimics the processes of DNA replication in the cell. Pribnow Decl. at ¶¶ 55-59; Pribnow 2nd Decl. at ¶¶ 13-17. When PCR is used in conjunction with a targeted segment of genomic DNA, numerous exact duplicates are synthesized, and these are indistinguishable in sequence and chemical composition from the targeted genomic DNA. *Id.*

PCR was developed in the 1980s by Dr. Kary Mullis at Cetus Corporation to develop exact duplicates—"amplicons"—of DNA segments. Pribnow Decl. at ¶ 16; Tait Decl. at ¶¶ 29-31. In 1989, the publication *Science* identified PCR and its use of a DNA polymerase from a thermophilic bacterium, *Thermus aquaticus* (*Taq* DNA polymerase), as the "Molecule of the Year," and Dr. Mullis won the Nobel Prize in Chemistry for his invention in 1993. Tait Decl. at ¶ 29. Thus, as the asserted patents acknowledge, PCR was a well-understood and routine activity in the scientific community prior to the time Myriad filed its August 1994 application corresponding to those asserted patents, and prior to the identification of the BRCA1 or BRCA2 gene sequences. *Id.* at ¶ 31; '441 Patent col.17 ll.21-37.

In any presently known process for analyzing a human's genes, the first step is to obtain a person's blood, saliva, or a cultured cell sample. DNA is then extracted from this sample. This extracted, genomic DNA represents a person's "diploid" genome, as it contains two copies of each autosomal (non sex chromosome) gene. Roa Decl. at ¶ 3; Pribnow Decl. at ¶ 55. The genomic DNA is then "fragmented," or cut into small pieces, often through sonication or biochemical shearing. The fragmentation randomly cuts all parts of the DNA into many

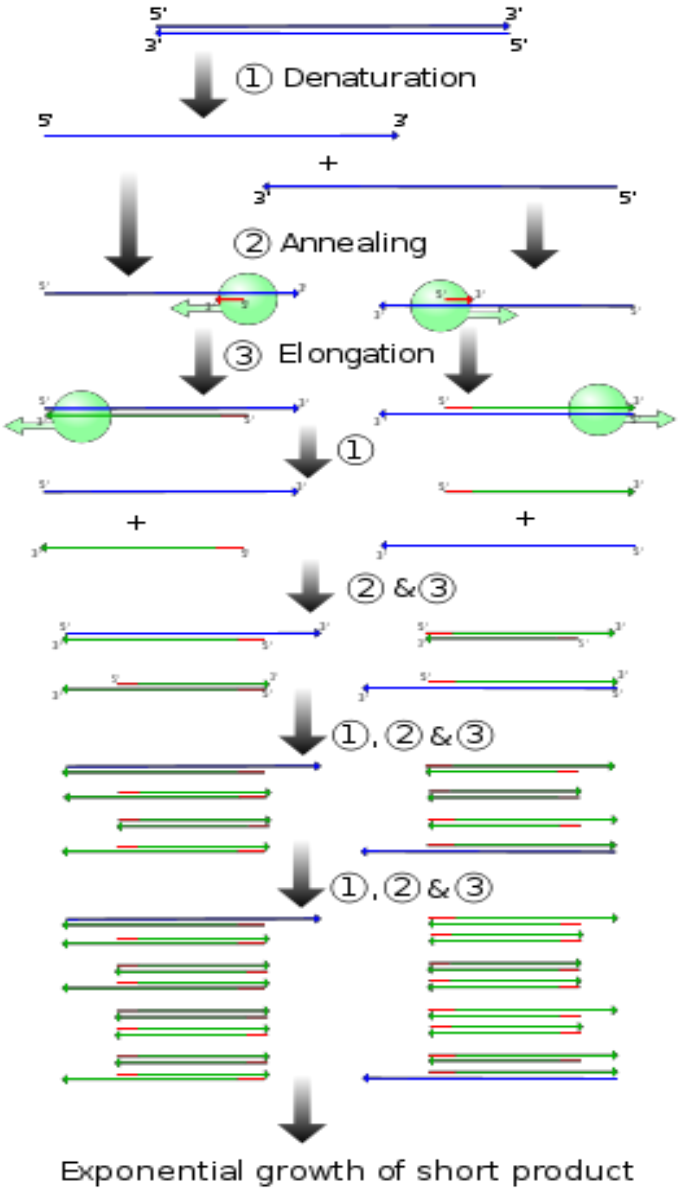
randomly sized pieces. These fragments are typically about 1000 nucleotides long, but smaller fragments can be created. Roa Decl. at ¶ 4; Pribnow Decl. at ¶ 55.

The PCR process begins by mixing the fragmented genomic DNA with: 1) a thermostable DNA polymerase enzyme; 2) a pool of all four DNA nucleotides (A, C, T and G); and 3) a great excess of single-stranded primer pairs. Kay Decl. at ¶ 32; Pribnow Decl. at ¶¶ 55-59; Pribnow 2nd Decl. at ¶¶ 13-17; Tait Decl. at ¶¶ 23-29. One primer in the pair is complementary to one end of the region to be amplified on one strand of the template DNA molecule and the other primer in the pair is complementary to the other end of the region to be amplified on the other strand of the template DNA. Kay Decl. at ¶ 32.[7]

Next, several steps occur in a cyclical reaction, as depicted in the illustration below. First, the template-primers mixture is heated so that the bonds linking the two strands of the template DNA molecule are overcome, causing the strands to separate. *Id*. at ¶ 33. This is called denaturation. *Id.* Second, the mixture is cooled enough to allow one copy of each primer to bind to its complementary template DNA sequence, in a process called annealing. *Id.* Third, the DNA polymerase adds nucleotides to the 3'-end of each of the primers in an order complementary to the template DNA. *Id.* This extension reaction results in the generation of a

[7] Some of the exon-only sequences in the BRCA1 and BRCA2 genes are so long that, when the entire gene is fragmented for PCR, some of the resulting fragments consist only of exons (i.e., they have no intron fragments). For instance, Exon 11 of BRCA1 is about 3,400 nucleotides long, while an exon segment in BRCA2 is about 5,000 nucleotides long. Roa Decl. at ¶ 14. Thus, the nucleotide sequence in the primer pairs necessary to amplify those exon fragments, and the resulting amplified DNA molecules or "amplicons," will inevitably share sequence similarity only with part of an exon in the gene. *Id*. at ¶¶ 13-15. Such large exons are likewise "too large to be encompassed within a single amplicon due to inherent limitations in the PCR process." As a result, the primer pairs are designed "to yield multiple distinct amplicons across the length of the gene" and, for large exons, multiple amplicons are tiled across the exon. *Id.* at ¶¶ 13-15.

copy of each strand of the template DNA—amplification. *Id.* The number of copied DNA molecules doubles with each PCR cycle. *Id.* A typical PCR runs for 20-30 cycles and results in the accumulation of millions of copies—amplicons—of the template DNA. *Id.*



It is essential that the amplicons contain exactly the same information contained in the DNA segment to be amplified, particularly where the amplicons will be used in testing. A patient and her doctor may make treatment decisions based on the information contained in the

patient's sequence of nucleotides, as reflected in the amplicons generated from her DNA. Aug. 23, 2013 Tutorial Tr. (Jackson) at 13:4-11, 23:16 – 24:3, 30:6 –31:13; Sept. 11, 2013 Hearing Tr. (Roa) at 112:4-17; Pribnow 2nd Decl. at ¶¶ 33-35. For example, whether the information in a woman's BRCA1 or BRCA2 genes predisposes her to an increased risk of hereditary breast or ovarian cancer can be determined by analyzing the sequence of at least portions of her BRCA1 and BRCA2 genes. The amplicons generated during PCR enable this evaluation. Sept. 11, 2013 Hearing Tr. (Roa) at 105:1-15, 111:20-25, 112:1-15; Pribnow Decl. at ¶¶ 64-70; Pribnow 2nd Decl. at ¶¶ 33-35.

7. Sequencing

After PCR, the resulting amplified DNA can be sequenced. This means that the specific nucleotide (adenine ("A"), thymine ("T"), cytosine ("C"), or guanine ("G")) in each position of the DNA is identified or "read." The identified sequence of an individual person's gene or genes is commonly called a "germline" sequence, meaning the gene sequence that a person inherited at birth. Roa Decl. at ¶ 24.

Two types of sequencing are at issue in this case: dideoxy sequencing (also known as Sanger sequencing) and Next-Generation Sequencing (NGS). Both types mimic DNA cell replication by using primers, DNA polymerase, and nucleotides—some of which have been chemically modified, but in ways that do not alter their Watson-Crick pairing functions. Aug. 23, 2013 Tutorial Tr. (Jackson) at 24:4-25; Elliott Decl. at ¶¶ 23-31; Tait Decl. at ¶¶ 35-36.

Sanger sequencing was developed in 1977 and is named for its inventor, Frederick Sanger.[8] NGS was not developed until the 2000s. Aug. 23, 2013 Tutorial Tr. (Roa) at 26:20 – 27:1; Sept. 11, 2013 Hearing Tr. (Roa) at 116:4-8; Tait Decl. at ¶¶ 35-37. Defendant's testing employs both Sanger sequencing and NGS. Elliott Decl. at ¶¶ 23-31; Elliott 2nd Decl. at ¶¶ 14-16; Tait Decl. at ¶¶ 35-36.

By the time Myriad submitted its first application corresponding to the asserted patents in August 1994, the laboratory techniques used to accomplish hybridization, amplification, and sequencing for the purpose of observing a genomic, or "native" gene sequence in a human sample were well understood, widely used, and fairly uniform insofar as any scientist engaged in obtaining the sequence of a gene in a human sample would likely have relied on the same techniques and general approach. Tait Decl. at ¶ 37. Likewise, the laboratory materials, reagents, and protocols to accomplish these tasks were well known and widely available in the art by that time, as the asserted patents acknowledge. Tait Decl. at ¶ 31;'441 Patent col.17 ll.20-27 ("These methods are well known and widely practiced in the art."). Plaintiffs' patents state that "the practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, and immunology." *See, e.g.,* '282 Patent col.25 ll.50-55.

a. Sanger Sequencing

Sanger sequencing includes, among other things, the application of artificial DNA nucleotide analogues known as dideoxynucleotide chain terminators to the amplified DNA.

[8] Mr. Sanger passed away on November 19, 2013. The sequencing method bearing his name was used to sequence the first human genome, the first draft of which was completed in 2000 after thirteen years of work. Sept. 11, 2013 Hearing Tr. (Roa) at 115:19-25; Elliott Decl. at ¶ 21.

Either the primers or the terminators have labels or tags, such as fluorescent dyes or radioactive phosphorus, that can be read during sequencing of the DNA to identify what type of nucleotide is present at each position in the gene. Roa Decl. at ¶ 25; Elliott Decl. at ¶¶ 35-39. Improvements in the Sanger method by 1987 led to automation of the sequencing process. These Sanger sequencing methods were widely used well before the first of Myriad's August 1994 applications corresponding to the asserted patents had been filed, and prior to the identification of the BRCA1 or BRCA2 gene sequences. Tait Decl. at ¶ 36.

b. Next Generation Sequencing (NGS)

NGS does not rely on the termination of DNA synthesis for resolution of a DNA's sequence. Unlike Sanger sequencing, NGS does not use dideoxy sequencing. Elliott Decl. at ¶¶ 24-25. Instead, DNA molecules are "sequenced by synthesis" through a process where tagged (e.g., fluorescent) nucleotides are added to a growing synthetic DNA molecule in a controlled, stepwise fashion. As nucleotides are incorporated into the new synthetic molecules, the corresponding tag is released. This release is detected by a machine utilizing a technology similar to a camera that detects the flash of the fluorescent tag. Each nucleotide (A, T, C, and G) has a unique color fluorescent tag attached so that the machine can detect which nucleotides were added, and in which order. Roa Decl. at ¶ 26; Elliott Decl. at ¶¶ 20, 24-25, 29-31.

8. Large Rearrangement Analysis

In addition to gene sequencing techniques like Sanger sequencing and NGS, scientists may also employ "large rearrangement analysis." This analysis enables scientists to determine if a person's gene contains large nucleotide deletions or sequence duplications which may not be observed during the sequencing processes described above.

Two common examples of large rearrangement analysis are multiplex ligation-dependent probe amplification (MLPA) and microarray. Roa Decl. at ¶ 30; Elliott Decl. at ¶¶ 40-42. Both MLPA and microarray processes use probes with a series of nucleotides precisely complementary to a piece of a single strand of the gene to be analyzed, such as BRCA1 or BRCA2 genes. MLPA uses pairs of probes that hybridize to adjacent segments of the target gene sequence and, after being hybridized, are chemically fused or "ligated" to form a single molecule. MLPA probes are chosen to be complementary to an "allele" in a gene, which refers to a form of the gene having a certain specific nucleotide sequence, such as a wild-type sequence, variant sequence, or mutation sequence of interest, and thus may be called a "wild-type" or a "mutated" allele. For large rearrangement testing, probes are targeted to parts of the gene that may contain deletions or duplications and are typically designed to detect deletion or duplication of one or more exons. Roa Decl. at ¶ 31; Elliott Decl. at ¶¶ 42-44, 47-52.

In the MLPA process, multiple synthetic probes are used containing various specific nucleotide sequences that target sequences of the parts of the gene to be analyzed (e.g., typically one pair of probes for each exon). The probes also include generic "primer tail" nucleotide sequences that allow for PCR probe amplification. MLPA probes are designed to assess large deletion or duplication mutations in or near coding exons in the gene. MLPA uses pairs of probes containing target gene sequences that are adjacent to each other. The probes hybridize to any of the DNA fragments that are complementary to those probes. Matching probes that hybridize next to each other are then ligated to form a longer oligonucleotide. Because the probes also have primer tail sequences, the resulting ligated DNA is then amplified through PCR and labeled with fluorescent tags. Roa Decl. at ¶ 32; *see* Elliott Decl. at ¶¶ 43-46. The resulting amplified MLPA products are analyzed and compared using computer software.

By comparing the relative copy number of MLPA products in a patient against a wild-type control, the presence of a large deletion or duplication can be detected. For example, if certain probes hybridize at approximately 50 percent the amount the hybridization obtained in a wild-type control, it means that there was no section of the gene to which those probes were complementary in one of the patient's expected two copies of the gene, indicating a deletion in the relevant region in one of the patient's copies of the gene. Conversely, a 50 percent increase in MLPA probes in a certain region indicates duplication of that region in the gene. Roa Decl. at ¶ 33; *see* Elliott Decl. at ¶¶ 46-48.

The hybridization of the probes is detected and quantified by amplification of the ligated longer probe. Conversely, if the region where the probe would normally hybridize has been deleted on one or more of the patient's chromosomes, then less-than-expected hybridization and ligation will take place and less than the expected amount of amplification will result. In this way, detecting hybridization, or the lack of hybridization, allows scientists to compare a patient's DNA sequence to a wild-type sequence and determine whether mutations are present. For this reason, using MLPA to detect an alteration in DNA necessarily requires detection of the wild-type allele through hybridization of the probes. Roa Decl. at ¶ 34; *see* Elliott Decl. at ¶¶ 46-48.

"Microarray," another form of large rearrangement analysis, uses a solid surface, such as a glass slide, with a collection of microscopic spots to which different DNA probes are attached. A microarray process employing comparative genomic hybridization (microarray-CGH) uses patient genomic DNA that is fragmented into small pieces. Synthetic products can be generated from the fragmented patient DNA by primer extension and labeling with a specific fluorescent dye. Similar products can be generated from fragmented wild-type DNA that is labeled with a different fluorescent dye. Alternatively, genomic fragments can be directly labeled with

fluorescent dyes. A mixture containing equal amounts of differentially labeled products representing patient genomic and wild-type DNA are hybridized to the microarray slide with immobilized probes tiled across the entire coding region of BRCA1 and BRCA2. Roa Decl. at ¶ 35; *see* Elliott Decl. at ¶¶ 51-53.

Following hybridization, the microarray slides are scanned and the relative dye intensities are analyzed and quantified. Equal amounts of the two dye signals indicate a normal result or, in other words, show that no large rearrangement has been detected. In contrast, if there is a relative decrease in the amount of patient's dye signal relative to wild-type dye signal, then deletion in one copy of the BRCA1 or BRCA2 gene regions covered by the affected probes is indicated. Conversely, if there is a relative increase in a patient's dye signal, then that result indicates a duplication of the gene region corresponding to those probes. The resulting data obtained in the microarray-CGH analysis allows for identification of large genomic deletions or duplications in the BRCA1 or BRCA2 genes. These large rearrangements can occur anywhere in the gene, and may involve a single exon, multiple exons, or even the entire gene coding region. Roa Decl. at ¶ 36; *see* Elliott Decl. at ¶ 53.

Microarray-CGH necessarily requires hybridization of sample DNA to a probe specific for the gene of interest, such as BRCA1 of BRCA2, and detection of that hybridization product. The resulting data allows identification of both the existence of the allele of interest and the existence of large mutations in a patient's germline sequence, i.e., comparing the sequence of the patient's BRCA1 or BRCA2 gene to wild-type, by comparing probe hybridization relative to the wild-type BRCA1 or BRCA2. Because the microarray process is performed by comparing the hybridization of the patient's allele to the hybridization of the wild-type allele,

this process necessarily requires detection of the wild-type allele through hybridization. Roa Decl. at ¶ 37.

C. The Race to Locate and Sequence BRCA1 and BRCA2

Breast cancer is by far the most often diagnosed type of cancer among women, affecting about one in eight women. Swisher Decl. at ¶ 19. Among the entire population of men and women combined, breast cancer is the second most diagnosed cancer.[9] The National Cancer Institute (NCI) estimates approximately 232,340 new cases of female breast cancer and 2,240 new cases of male breast cancer will have been diagnosed in the United States in 2013. *Id*. The NCI estimates that breast cancer will have caused approximately 39,620 female deaths and 410 male deaths in the United States in 2013. *Id.* Ovarian cancer is the eighth most common cancer in women. Although less common than breast cancer, it causes more deaths in the Western world than any other gynecologic cancer. *Id*. at ¶ 21.

In the 1980s, breast cancer patients mobilized to increase public awareness of the breast cancer epidemic. Due to these efforts and those of breast cancer organizations, the Department of Defense created a research program devoted to breast cancer research. Between 1990 and 2008, the annual funding for this research increased from $90 million to $2.1 billion. Parthasarathy Decl. from *AMP* Litigation at ¶ 10 (Dkt. 34-7).

Also during the 1980s, scientists from the United States, England, France, Germany, Japan, and other countries were competing to first identify the nucleotide sequences linked to breast cancer. In 1989, various European and American research laboratories participated in an International Breast Cancer Linkage Consortium. *Id.* at ¶ 11.

[9] *See* <http://www.cancerresearchuk.org/cancer-info/cancerstats/world/breast-cancer-world/>.

In 1990, a research group led by Mary-Claire King at the University of California, Berkeley announced that it had discovered that the Breast Cancer Susceptibility Gene 1 (BRCA1) was located on chromosome 17. With this discovery, research teams around the world intensified efforts to be the first to sequence the BRCA1 gene. *Id.* at ¶ 11. Among them were different teams led by Dr. King; Dr. Mark Skolnick, co-founder of Myriad; and Dr. Michael Stratton of the Institute for Cancer Research, London (ICR). *Id.*

In September 1994, Dr. Skolnick's group at Myriad—including researchers from the National Institute for Environmental Health (NIEH), an agency of the National Institutes of Health (NIH)—announced that they had sequenced the BRCA1 gene. *Id.* at ¶ 11. They won a hard-fought "race," as journalists reported at the time:

> The race to find the breast-cancer gene has been one of the most closely-watched and publicized of a host of gene hunts in recent years. The pursuit of the gene was triggered in late 1990 when Mary-Clare King, a geneticist at the University of California at Berkeley, stunned the cancer-research community by pinpointing the the [sic] gene's approximate location. About a dozen laboratories around the world, including Dr. King's, have been intensely probing a tiny region of genetic material since then. In the past few months, scientists said they had identified about 30 genes in the approximate region but had pared the search down to about four to six likely culprits. Dr. Skolnick said the first hint they had latched onto the gene came about two months ago. Since then they have worked to identify its structure.

Scientists Say They've Found Gene That Causes Breast Cancer, The Wall Street Journal, September 14, 1994 (Dkt. 114-2). By the time this discovery was publicly announced in September 1994, Myriad had applied for patents related to BRCA1, including the '282 and '441 Patents.[10]

After the sequencing of BRCA1, many scientists thought there was at least one more gene linked with breast cancer, and the search for that gene continued. *Id.* at ¶ 12. By 1994, the

[10] These patents have the priority date of August 12, 1994, and begin to expire in August 2014.

existence of a 'BRCA2 gene' and its location on chromosome 13q was known, as described by Plaintiffs in the background of the invention section of the '441 Patent:

> Intense efforts to isolate the BRCA1 gene have proceeded since it was first mapped in 1990. [citations omitted]. A second locus, BRCA2, has recently been mapped to chromosome 13q (Wooster et. al., 1994) and appears to account for a proportion of early-onset breast cancer roughly equal to BRCA1, but confers a lower risk of ovarian cancer.

'441 Patent col.2 l.46—col.3 1.4.

In December 1995, the group led by Dr. Mark Stratton announced they had mapped and sequenced the elusive second gene, the BRCA2 gene, which was linked to incidence of ovarian cancer, as well as female and male breast cancer. Parthasarathy Decl. from *AMP* Litigation at ¶ 12. The day before the Stratton group published the BRCA2 gene sequence in the scientific journal, *Nature*, however, Myriad announced that it too had found the BRCA2 gene. *Id.* Myriad submitted its sequence to GenBank, an international depository of gene sequence information, and applied for patents on the BRCA2 gene in the United States and Europe. *Id.*

The sequencing of the BRCA1 and BRCA2 genes were landmark events in genetics, as mutations in these genes are responsible for many breast and ovarian cancer cases. About 10 percent of breast cancers are inherited genetically, about 5 percent as a result of a BRCA1 or BRCA2 genetic mutation. Swisher Decl. at ¶ 20. Individuals with BRCA1 and BRCA2 mutations have about a 45 to 87 percent risk of developing breast cancer by age 70. *Id.* Between 20 to 25 percent of ovarian cancers are inherited genetically. For women with inherited ovarian cancer, 75 percent of them can attribute the cancer to either BRCA1 or BRCA2. About 50 percent of inherited ovarian cancers are caused by BRCA1 mutations, about 25 percent are caused by BRCA2 mutations, and the remaining 25 percent are caused by other genes. Women with inherited BRCA1 mutations have a 40 to 52 percent cumulative risk of ovarian cancer by

the time they reach 70 years old. For women with inherited BRCA2 mutations, the risk is approximately 15 to 25 percent. *Id.* at ¶ 22. Very little can be done for patients once diagnosed with ovarian cancer, making preventive care vital. *Id.* at ¶ 23.

D. Myriad's Testing Products: BRACAnalysis, BART, and myRisk

Beginning in 1994 and continuing for several years, Myriad obtained numerous patents related to BRCA1 and BRCA2. By 1996, it began to market BRCA1 and BRCA2 molecular testing products. That year, Myriad introduced BRACAnalysis, a molecular diagnostic test used to detect the presence and characterization of 'point' or small mutations in the BRCA1 or BRCA2 gene that are responsible for a majority of hereditary breast and ovarian cancers. Ford Decl. at ¶¶ 1, 3; Sept. 12, 2013 Hearing Tr. (Ford) at 312:5-25 (Dkt. 151). The BRACAnalysis test does not include large rearrangement testing for BRCA1 and BRCA2—testing that can identify initially false negative results in a BRACAnalysis point mutation test.

Myriad offers an additional test that provides large rearrangement testing for the BRCA1 and BRCA2 genes, called BRACAnalysis Rearrangement Test, or "BART." Sept. 12, 2013 Hearing Tr. (Ford) at 312:19-25. But a patient who obtains Myriad BRACAnalysis testing does not automatically get follow-up BART testing. *Id.* at 101:22-52:15; Swisher Decl. at ¶¶ 97-98; Matloff Decl. at ¶ 7 (Dkt. 49). If a patient does not satisfy Myriad's criteria for being at high risk of a large rearrangement mutation in her BRCA1 and BRCA2 genes, or if her insurance does not cover BART, then the patient must pay for the BART test separately. Sept. 12, 2013 Hearing Tr. (Ford) at 314:2-9. According to a 2013 peer-reviewed study in the *Journal of Clinical Oncology*, Myriad's criteria for providing BART large rearrangement testing automatically as part of its BRCA testing does not cover half the patients who have large rearrangement mutations: "[f]ewer than half of the large rearrangement carriers in the present study met Myriad Genetics

Laboratories' criteria . . . for automatic large rearrangement testing." Chao Decl. at Exh. P at 212 (Weitzel *et al*., 31(2) J. Clin. Oncol. 210-06 (2013)).

The current list price for BRACAnalysis is $3,340 and the list price for BART is $700. Sept. 12, 2013 Hearing Tr. (Ford) at 313:11-15. Together, the list price for both tests is $4,040. Ford. Decl. at ¶ 11. Those who get BART in addition to BRACAnalysis are billed separately for the two tests. Pls.' Reply Br. at 135. But not all of Myriad's patients have insurance coverage for BART. Mark C. Capone, President of Myriad Genetic Laboratories, Inc., suggested on May 7, 2013, that approximately 20 percent of patients receiving BRACAnalysis did not have insurance coverage for BART. Sept. 12, 2013 Hearing Exh. 3 at 15 (Dkt. 144-2) ("Our Managed Care team continued to make significant progress on BART reimbursement in the fiscal third quarter and we ended the quarter with reimbursement coverage for approximately 80 percent of patients."). Because BART is not automatically included as part of Myriad's BRCA1 and BRCA2 testing, some patients must pay the $700 out-of-pocket for BART if they are to get that testing.

On September 5, 2013, Myriad announced a limited launch of myRisk, a new "multi-gene diagnostic test that will provide increased sensitivity by analyzing 25 genes associated with eight major cancers including: breast, colorectal, ovarian, endometrial, pancreatic, prostate, gastric and melanoma." Myriad Press Release, Sept. 5, 2013.[11] This test utilizes the Next-Generation Sequencing used by Defendant and tests for 24 of 25 of the same genes as Defendant's CancerNext panel. Chao Decl. at ¶¶ 46-47 and Exh. I. In an investor and analyst presentation given on May 9, 2013, Myriad described myRisk as a "significant improvement of BRACAnalysis." *Id*. at ¶ 45, Exh. I at 19-45. Similarly, in a press release dated May 30, 2013,

[11] *See* <http://investor.myriad.com/releasedetail.cfm?ReleaseID =788983>.

Myriad stated: "myRisk represents a scientific advancement that will revolutionize hereditary cancer testing for appropriate patients." *Id*. at Exh. J at 1.

For the time being, it appears that this launch provides limited access to the public, as it is for "a limited number of medical and scientific thought leaders":

> myRisk Hereditary Cancer is being launched in a phased approach beginning with an early-access, clinical-experience program to a limited number of medical and scientific thought leaders followed by an expanded access program later in the year. The Company will present extensive clinical validity data for myRisk Hereditary Cancer at The Collaborative Group of the Americas on Inherited Colorectal Cancer (CGA) annual meeting in October and the San Antonio Breast Cancer Symposium in December.

Myriad Press Release, Sept. 5, 2013.

E. The *AMP* Litigation

1. Judge Sweet's Decision—Southern District of New York

A group of medical organizations and individuals sued Myriad in 2009, challenging fifteen composition and method claims in seven of Myriad's BRCA1 and BRCA2-related patents on the grounds that they were drawn to products of nature and mental processes—subjects that are patent ineligible under 35 U.S.C. § 101. *Association for Molecular Pathology v. United States Patent and Trademark Office*, 702 F. Supp. 2d 181, 186 (S.D.N.Y. 2010).[12] These patents were drawn to "(1) isolated DNA containing all or portions of the BRCA1 and BRCA2 gene sequence and (2) methods for 'comparing' or 'analyzing' BRCA1 and BRCA2 gene sequences to identify the presence of mutations correlating to breast or ovarian cancer." *Id.* at 184. United States District Court Judge Robert W. Sweet characterized the overarching issue

[12] Specifically at issue in *AMP* were claims 1, 2, 5, 6, 7, and 20 of the '282 Patent; claims 1, 6, and 7 of the '492 Patent; claim 1 of U.S. Patent 5,693,473 (the '473 Patent); claim 1 of the '999 Patent; claim 1 of U.S. Patent 5,710,001 (the '001 Patent); claim 1 of the '441 Patent; and claims 1 and 2 of the '857 Patent.

presented as: "[a]re isolated human genes and the comparison of their sequences patentable?" *Id.* at 185. Judge Sweet answered that question in the negative and granted summary judgment in favor of the plaintiffs. *Id.* at 185.

Judge Sweet construed "isolated DNA" to mean a "segment of DNA nucleotides existing separate from other cellular components normally associated with native DNA, including proteins and other DNA sequences comprising the remainder of the genome, and includes both DNA originating from a cell as well as DNA synthesized through chemical or heterologous biological means." *Id.* at 217. He concluded that neither Myriad's isolated DNA (composition) claims, nor its method claims were drawn to patent eligible subject matter.

The composition claims turned on the issue of "whether or not claims directed to isolated DNA containing naturally-occurring sequences fall within the products of nature exception to § 101." *Id.* at 220. As a starting point, Judge Sweet noted that "Supreme Court precedent has established that products of nature do not constitute patentable subject matter absent a change that results in the creation of a fundamentally new product." *Id.* at 222. Even "'purification' of a natural compound, without more, is insufficient to render a product of nature patentable." *Id.* at 223. Judge Sweet rejected Myriad's argument that "purified DNA" is necessarily patent eligible because DNA doesn't exist in nature in a purified form. *Id.* at 224. Observing that even a "purified product" must have "'markedly different characteristics' in order to satisfy the requirements of § 101," Judge Sweet analyzed whether Myriad's "isolated DNA" had "'markedly different characteristics' from a product of nature." *Id.* at 227-28 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980)).

Myriad, citing the "chemical nature of DNA," argued that isolated DNA "is 'markedly different' from DNA found in nature" due to "structural and functional" differences. *Id.* at 228.

For example, Myriad pointed out that there are chromosomal proteins associated with native DNA that are not associated with isolated DNA. *Id.* at 229-30. But Judge Sweet found that focusing on these differences ignores the reason DNA is unique from other chemical compounds in nature—because it encodes and conveys information:

> The information encoded in DNA is not information about its own molecular structure incidental to its biological function, as is the case with adrenaline or other chemicals . . . . Rather, the information encoded by DNA reflects its primary biological function: directing the synthesis of other molecules in the body—namely, proteins. . . . DNA, and in particular the ordering of its nucleotides, therefore serves as the physical embodiment of laws of nature—those that define the construction of the human body. . . . Consequently, the use of simple analogies comparing DNA with chemical compounds previously the subject of patents cannot replace consideration of the distinctive characteristics of DNA.

Id. at 228-29. It is DNA's nucleotide sequence that is critical to both its "natural biological function" and "the utility associated with DNA in its isolated form." *Id.* at 229.

Judge Sweet also rejected Myriad's argument that isolated DNA is distinct from native DNA insofar as it "may be used in applications for which native DNA is unsuitable, namely, in 'molecular diagnostic tests (e.g., as probes, primers, templates for sequencing reactions), in biotechnological processes (e.g. production of pure BRCA1 and BRCA2 protein), and even in medical treatments (e.g. gene therapy).'" 702 F. Supp. 2d at 230-31 (quoting Myriad's *AMP* Reply Br. in Support of Motion for Summary Judgment at 9 (other citations omitted)). Judge Sweet noted that the cited applications depend on the single-stranded isolated DNA segment having "the identical sequence as the complementary DNA strand to the DNA strand containing the target DNA sequence." *Id.* at 231, n.54. The BRCA-specific nucleotide sequence is "the defining characteristic of the isolated DNA that will always be required to provide the sequence-specific targeting and protein coding ability that allows isolated DNA to be used for the various applications cited by Myriad." *Id.* at 232.

Judge Sweet found unpersuasive Myriad's contention that it "created" the claimed BRCA DNA molecules when it identified the "specific segments of chromosomes 17 and 13 that correlated with breast and ovarian cancer (BRCA1 and BRCA2) and isolated "these sequences away from other genomic DNA and cellular components." *Id.* at 232. Rather than "creating" BRCA, the court concluded that Myriad merely discovered it. While discovery of the "important correlation" was a "valuable scientific achievement" requiring "technical skill and considerable labor," it was, nevertheless, a "discovery of the handiwork of nature—the natural effect of certain mutations in a particular segment of the human genome." *Id.* at 232. For those reasons, Judge Sweet concluded that despite Myriad's cited structural and functional differences between "native DNA" and "isolated DNA," the two were not "markedly different" from one another. Myriad's composition claims were patent ineligible, as they were directed to natural phenomena.

Judge Sweet next analyzed Myriad's method claims, drawn to 1) analyzing and comparing DNA sequences to determine the existence of BRCA1 and BRCA2; and to 2) screening cancer therapeutics by comparing the growth rate of cells when a test compound is added to one cell group. With the law as it was at the time before the Supreme Court's pronouncements in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.,* 132 S. Ct.

1289 (2012) and *Bilski v. Kappos*, 130 S. Ct. 3218 (2010)[13] Judge Sweet applied the 'machine or transformation' test to find that all of the challenged method claims were drawn to mental processes and lacked any transformative step or machine. *Id.* at 235-37. Myriad argued that its act of "isolating and sequencing DNA" was transformative, and although not explicitly included, should be read into the 'sequence and analyze' method claims.

The court concluded that the "preparatory steps" of isolating and sequencing could not be read into the claims—but even if they were, they "would constitute no more than 'data-gathering step[s]' that are not 'central to the purpose of the claimed process.'" *Id.* at 236 (quoting *Bilski v. Kappos*, 545 F.3d 943, 962-63 (Fed. Cir. 2008), *aff'd on other grounds*, *Bilski*, 130 S. Ct. 3218). Likewise, with regard to the 'comparing growth cell rate' claims, Judge Sweet concluded the claimed 'process' was "in fact, the scientific method itself," an unpatentable mental process under § 101. *Id.* at 237.

2. Federal Circuit *AMP* Opinions

Myriad appealed Judge Sweet's decision to the Federal Circuit Court of Appeals. In July 2011, the Federal Circuit affirmed Judge Sweet's conclusion that Myriad's "analyze and

[13] At the time of Judge Sweet's decision, many courts viewed the machine or transformation test as dispositive when analyzing § 101 challenges to process, or method claims. The Supreme Court in *Bilski* clarified that although the test provides important clues as to patent eligibility, is not categorically dispositive. 130 S. Ct. at 3230. In *Bilski*, the Court considered whether a claimed "process" of risk hedging—reduced in the claims to a mathematical formula—was a patent ineligible abstract idea. The Court noted that business processes may, in some cases, be patentable. Still, it found the formula there at issue to be a patent ineligible abstract idea. *Id.* at 3231. The Court was concerned with allowing a patent on the risk-hedging method based on the formula, where a patent would "pre-empt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea." *Id.*

compare" method claims were drawn to patent ineligible subject matter, but it reversed on the other issues. 653 F.3d 1329, 1350, 1355-56, 1358 (Fed. Cir. 2011). The Federal Circuit concluded that Myriad's "isolated DNA" composition claims (including a subset of claims drawn to cDNA) and its method claim covering cancer therapeutic comparisons were patent eligible. *Id.* at 1357-58. The *AMP* plaintiffs successfully petitioned the Supreme Court for a writ of certiorari. 132 S. Ct. 1794 (2012). The Court vacated the Federal Circuit's decision and remanded the case for further consideration in light of the Supreme Court's then-recent decision in *Mayo*, 132 S. Ct. 1289.

On remand, the Federal Circuit reached conclusions identical to those in its prior decision. 689 F.3d 1303, 1337 (2012). In an opinion authored by Judge Lourie, two members of the three judge panel concluded that Myriad's composition claims were drawn to patent eligible subject matter—but the judges did not agree on the reasons for this result. The court again found patent eligible Myriad's lone method claim relating to comparison of cell growth with or without added therapeutics. *Id.* at 1335-37. Finally, as it had before, the court concluded that Myriad's method claims for analyzing and comparing DNA sequences were drawn to patent ineligible subject matter. *Id.* at 1334-35.

First, concerning the composition claims, the court cited three representative claims from the '282 Patent: 1) claim 1, covering "isolated DNA coding for a BRCA1 polypeptide"; 2) claim 2, covering the "isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in" BRCA1 cDNA; and 3) claim 5, covering an "isolated DNA having at least 15 nucleotides of the DNA of claim 1." *Id.* at 1309. Myriad argued that an isolated DNA molecule claimed in each is "patent eligible because it is . . . 'a nonnaturally occurring manufacture or composition of matter' with a distinctive name, character and use.'" *Id.* at 1325 (quoting

Myriad's Appellant Brief, 2010 WL 4600106, at *41-42 (other citations omitted)). Myriad asserted that Judge Sweet had 1) mistakenly applied Supreme Court precedent to exclude from patent eligibility all products of nature unless "markedly different" from "naturally occurring" products; and 2) incorrectly focused on the informational content similarity between native DNA and isolated DNA, instead of their claimed differences. Buttressing these points, Myriad argued that "isolated DNA does not exist in nature and that isolated DNAs, unlike native DNAs, can be used as primers and probes for diagnosing cancer." *Id.* at 1325.

Plaintiffs disagreed, arguing the isolated DNA Myriad claimed was not markedly different from native DNA, despite Myriad's asserted structural differences, because it "retain[s] part of the same nucleotide sequence . . . ." *Id.* at 1326. Further, the plaintiffs warned that if allowed, Myriad's composition claims would "preempt products and laws of nature, excluding anyone from working with the BRCA genes and the genetic information they convey." *Id.*

The United States, as amicus curiae, staked out a "middle ground," arguing that one sub-category of Myriad's claimed isolated DNA, synthetic cDNA, was patent eligible, while the remainder were not. To reach this result, the government proposed viewing the challenged claims through the lens of a so-called 'magic microscope': if one using "an imaginary microscope could focus in on the claimed molecule as it exists in the human body, the claim covers ineligible subject matter." *Id.* at 1326. Applying this test, cDNA would be patent eligible, because it is "engineered by man to splice together non-contiguous coding sequences (i.e., exons)." *Id.* at 1325-26. But "the claimed isolated BRCA1 and BRCA2 sequences" would be patent ineligible, because the nucleotide sequences comprising those genes appear in the body just as they do in the isolated DNA. *Id.* at 1326.

Judges Lourie and Moore found non-cDNA isolated DNA patent eligible, while Judge Bryson concluded it was not. Judge Lourie wrote that all of Myriad's claimed isolated DNA was markedly different from native DNA "in name, character and use." *Id.* at 1328 (quoting *Chakrabarty*, 447 U.S. at 309-310). According to Judge Lourie, the district court was incorrect to focus on the identical nucleotide sequence and informational content in native and isolated DNA because "it is the distinctive nature of DNA molecules as isolated compositions of matter that determines their patent eligibility rather than their physiological use or benefit . . . their informational content is irrelevant." *Id.* In addition to being "free-standing," and "cleaved," isolated DNA may be shorter than native DNA—"synthesized to consist of just a fraction of a naturally occurring DNA molecule"—and thus include "primers and probes, having as few as fifteen nucleotides of a BRCA sequence." *Id.* at 1328.

Writing separately, Judge Moore disagreed with Judge Lourie that isolated DNA—aside from cDNA—was patent eligible simply because of "the chemical differences between genomic and isolated DNA (breaking the covalent bonds) . . . ." *Id.* at 1341. Judge Moore concluded that shorter isolated DNA was patent eligible because it possessed the unique utility of being capable of use as primers or probes, and was thus markedly different from naturally occurring DNA. In contrast, Judge Moore expressed concern about the patent eligibility of longer strands of isolated DNA, observing that if she were "deciding [the] case on a blank canvas," she would have found those longer strands, unsuitable for use as primers or probes, patent ineligible. *Id.* at 1343. But, out of deference to the United States Patent and Trademark Office (USPTO) then-existing practice of granting patents on isolated genes and the reliance of those who hold those patents, Judge Moore joined in Judge Lourie's result and concluded that all isolated DNA was patent eligible. *Id.*

Judge Bryson dissented from the panel's conclusion that isolated DNA was patent eligible. *Id.* at 1348. Guided by the Supreme Court's *Chakrabarty* decision, Judge Bryson focused "on two things: 1) the similarity in structure between what is claimed and what it found in nature[;] and 2) the similarity in utility between what is claimed and what is found in nature." *Id.* at 1354. Regarding structure, Judge Bryson concluded that the isolated BRCA genes were not rendered patent eligible simply because they were purified and their bonds cleaved in order to extract them. Like an extracted mineral, a cutting from a plant, or a kidney removed from a body, the only "material change made to these genes from their natural state is the change that is necessarily incidental to [their] extraction . . . ." *Id.* at 1350.

That their chemical makeup changes when the bonds are broken does not compel the conclusion that a new molecule is created, as "there is no magic to a chemical bond that requires us to recognize a new product when a chemical bond is created or broken, but not when other atomic or molecular forces are altered." *Id.* at 1349. This is particularly so where Myriad's composition claims, aside from cDNA, are not "defined by any particular chemical formula." *Id.* The fact that isolated DNA has different "terminal groups" than those on naturally occurring genes is insignificant in light of the critical function of DNA—which is "dictated by the nucleotide sequence of the gene—a sequence that is determined by nature and that appears in nature exactly as it appears in the claimed isolated DNA." *Id.* at 1352. Likewise, that the isolated DNA was a smaller part of a naturally larger molecule was of no moment—Judge Bryson found this no more persuasive "than arguing that although an atom may not be patentable, a subatomic particle is patentable because it was previously part of a larger structure." *Id.* at 1353.

In short, Judge Bryson found the structural differences between the isolated BRCA DNA and native genes "irrelevant to the claim limitations, to the functioning of the genes, and to their utility in their isolated form. . . [i]ndeed, that identity of function in the isolated gene is the key to its value." *Id.* at 1354. The "informational content of the nucleotide sequences is the critical aspect of these molecules . . . ." *Id.* at 1355. Thus, the fact that the "nucleotide sequences of the claimed molecules are the same as the nucleotide sequences found in naturally occurring human genes" outweighed the ancillary structural differences. *Id.*

Though they disagreed on isolated non-cDNA DNA, the Federal Circuit panel agreed that cDNA was patent eligible. Judge Lourie analyzed cDNA as a sub-category of isolated DNA, concluding that cDNA was even more distinctive from native DNA than other isolated DNA, as cDNA lacks "the non-coding introns present in naturally occurring chromosomal DNA." *Id.* at 1329. Judge Moore joined in this part of the opinion. Judge Bryson concurred, generally agreeing that cDNA could be patent eligible as a "human-made invention" with both distinct structure and utility from naturally occurring DNA. *Id.* at 1356 (noting cDNA's lack of introns and the fact that it can be attached to a promoter and inserted into non-human cell to drive protein expression). But Judge Bryson noted issues with two of Myriad's claims to short segments of DNA—claims 5 and 6 of the '282 Patent. Claim 5 covers any segment of DNA defined by claim 1 (isolated DNA coding for BRCA1) at least 15 nucleotides in length, while claim 6 covers any sequence of BRCA1 (exon only) cDNA at least 15 nucleotides long. Judge Bryson noted that claim 6 would encompass "each BRCA1 exon, even though each is naturally defined by transcription." *Id.* at 1356. Further, the claim would cover exon-only portions of "more than 4% of human genes." *Id.* Given its breadth, Judge Bryson concluded claim 6 was necessarily drawn to patent ineligible products of nature. *Id.* at 1356.

Though the Federal Circuit found isolated DNA and cDNA patent eligible, it nevertheless found all but one of Myriad's asserted method claims to be patent ineligible as claiming only "abstract mental processes" of "comparing" or "analyzing" BRCA sequences. *Id.* at 1334 (citing *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)). These claims were not rescued by the fact that the claimed comparisons were limited to the context of BRCA genes or particular alterations. *Id.* (quoting *Bilski*, 130 S. Ct. at 3230 ("prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.'")) (other citations omitted). Further, like the district court, the Federal Circuit refused to allow Myriad to read into these claims the "additional, allegedly transformative steps" of extracting DNA from a human sample and sequencing the BRCA DNA. *Id.* at 1335. The steps were simply not included in the method claims. *Id.* Rather, the court noted that Myriad's 'compare' and 'analyze' steps were even less transformative than the 'administer' and 'determine' steps in *Mayo*, which were also found to be patent ineligible. *Id.*

Myriad's lone-surviving method claim was claim 20 of the '282 Patent, directed to screening potential cancer therapies by comparing cell growth rates in the presence of different compounds. *Id.* at 1335. Following *Mayo*, the panel found this claim patent eligible where 1) the court had concluded that BRCA genes were patent eligible in the first instance, and 2) it involved a transformative step of growing "host cells transformed with an altered BRCA1 gene." *Id.* at 1336. The court explained that "[t]he transformed, man-made nature of the underlying subject matter in claim 20 makes the claim patent-eligible," and the fact that the claim also included mental steps of determining and comparing growth rates would not alter that conclusion. *Id.*

3. Supreme Court Decision

The *AMP* plaintiffs again appealed their loss on Myriad's composition claims to the Supreme Court. Myriad did not cross-appeal their invalid method claims. On June 13, 2013, the Court issued a unanimous opinion holding "that a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated." 133 S. Ct. at 2111. In contrast, it found that cDNA could be patent eligible "because it is not naturally occurring." *Id.*.

In reaching its decision, the Court first reviewed the science underlying the case, noting that scientists could, "using well known methods," 1) extract DNA from cells, allowing them "to isolate specific segments of DNA . . . which can then be further studied, manipulated, or used"; and 2) create DNA synthetically . . . ." *Id.* at 2112. "One such method" for creating synthetic DNA, using mRNA to create cDNA, "results in the inverse of the mRNA's inverse image of the original DNA, with one important distinction: Because the natural creation of mRNA involves splicing that removes introns," the synthetic cDNA "contains only the exon sequences." *Id.* at 2112.

The Court then reviewed the lower court decisions, including the Federal Circuit's determination "that both isolated DNA and cDNA were patent eligible under § 101." *Id.* at 2115. Here, the Court noted that Judge Lourie supported his decision that isolated DNA was chemically different from genomic DNA, and therefore patent eligible, by stating, "[i]solated DNA has been cleaved . . . or synthesized to consist of just a fraction of a naturally occurring DNA molecule." *Id.* at 2115 (quoting 689 F.3d at 1328). The Court also quoted Judge Bryson's opinion in which he observed that "the structural similarity dwarfs the significance of the structural differences between isolated DNA and naturally occurring DNA, especially where the

structural differences are merely ancillary to the breaking of covalent bonds, a process that is itself not inventive." *Id.* at 2115 (quoting 689 F.3d at 1355).

Turning to its own analysis of Myriad's isolated DNA claims, the Court first observed that Myriad did not "create or alter": 1) "any of the genetic information encoded in the BRCA1 and BRCA2 genes," as the "location and order of the nucleotides existed in nature before Myriad found them"; or 2) "the genetic structure of DNA." 133 S. Ct. at 2116. In contrast to inventions with "markedly different characteristics from any found in nature," the Court identified Myriad's "contribution" as "uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13." *Id.* (citing *Chakrabarty*, 447 U.S. at 305). While important, useful, and achieved through "extensive research efforts," this was "not an act of invention." *Id.* at 2117-19 (noting "extensive effort alone is insufficient to satisfy the demands of § 101" and that the processes used by Myriad to isolate DNA were well understood by geneticists at the time of Myriad's patents.). Taken together, Myriad's discovery fell "squarely within the law of nature exception" to patent eligibility under § 101. *Id.*

Critically, the Court found that Myriad's isolated DNA claims could not be saved "by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule." *Id.* This was because Myriad's claims were "not expressed in terms of chemical composition," nor did they rely on "chemical changes that result from the isolation of a particular section of DNA." *Id.* at 2118. Instead, the claims were focused on "the genetic information encoded in the BRCA1 and BRCA2 genes . . . Myriad's claim is concerned primarily with the information contained in the genetic *sequence*, not with the specific composition of a particular molecule." *Id.* at 2118 (emphasis in original).

Finally, the Court dismissed Myriad's contention that the USPTO's decision to grant its patents warranted deference. The Court noted that Congress had not only failed to endorse with legislation the type of patents at issue, but also the government had actually taken the position before the Court and the Federal Circuit "that isolated DNA was *not* patent eligible under § 101." *Id.* at 2119 (emphasis in original). Thus, the Court found Myriad's claimed "genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material." *Id.* at 2120.

In contrast, the Court found that cDNA may be patent eligible under § 101. Unlike naturally occurring, isolated DNA segments, "cDNA differs from natural DNA in that 'the non-coding regions [introns] have been removed.'" *Id.* at 2119. A "lab technician unquestionably creates something new when cDNA is made." *Id.* Accordingly, cDNA generally is "distinct from the DNA from which it was derived" and "not a 'product of nature.'" *Id.* But, cDNA's patent eligibility is not without exception. The Court explained that cDNA may be a patent ineligible product of nature when "very short series of DNA may have no intervening introns to remove when creating cDNA." *Id.* In that circumstance, "a short strand of cDNA may be indistinguishable from natural DNA," and presumably not patentable. *Id.* at 2119.

In this respect, the Court's decision echoes Judge Bryson's opinion. Perhaps the Court utilized, without expressly stating, a test similar to the 'magic microscope' urged by the government before the Federal Circuit. The Court's ruling comports with the government's position before the Federal Circuit.

F. Defendant's BRCA1 and BRCA2 Testing

On June 13, 2013, the day the Supreme Court issued its *AMP* decision, Defendant announced that it would begin offering BRCA1 and BRCA2 testing. Ford Decl. at ¶ 9.[14] Defendant invested an estimated $46.7 million in capital resources, expanding its laboratory and hiring an additional 110 employees, to be positioned to offer the first comprehensive multi-gene hereditary test for breast and ovarian cancer. Hampton Decl. at ¶ 57 (Dkt. 58); Chao Decl. at ¶¶ 71-73.

Defendant has released a Cancer Test Requisition Form that offers multiple tests BRCA1 and/or BRCA2 tests. Ford Decl. at Exh. 1. Defendant sequences all coding exons, plus "at least 5 bases into the 5′ and 3′ ends of all the introns and untranslated regions."[15] Defendant's tests use primers that amplify the sequences of the exons and at least 20 base pairs of the introns, and the amplicons are sequenced by Next Generation Sequencing. Elliott Decl. at ¶¶ 10, 20-31. Defendant also performs Sanger sequencing as verification of its Next-Generation sequencing to confirm all identified variants or to obtain an additional result if there are parts of the exon that do not have a sufficient number of reads to ensure accuracy. Here, Defendant "sequences the exon or part of the exon in which the variant was detected."[16]

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[14] *See* <http://ambrygen.com/tests/brcaplus-%E2%80%93-high-risk-breast-cancer-panel>.

[15] *See* Defendant's Data Sheets for BreastNext (Dkt. 10 at Exh. D at 4-5); CancerNext (*id.* at Exh. E at 6); OvaNext (*id.* at Exh. F at 5); BRCA1/BRCA2 (*id.* at Exh. I at 2): BRCAplus tests (*id*. at Exh. L at 3); Defendant's NextGen PowerPoint (*id*. at Exh. J at 10-12, 26); RainDance Target Sequencing Assay Manual (*id.* at Exh. K at A-3 to A-7, 3-2, 4-2, 5-2); Elliott Decl. at ¶¶ 10, 20-31.

[16] Elliott 2nd Decl. at ¶ 16; *see also* Elliott Decl. at ¶ 35; Defendant's NGS Cancer Panels PowerPoint (Dkt. 10 at Exh. B at 4); Defendant's Poster (*id.* at Exh. C); Defendant's Data Sheets for BreastNext (*id*. at Exh. D at 5), CancerNext (*id*. at Exh. E at 6), OvaNext (*id.* at Exh. F at 6), BRCA1/2 (*id.* at Exh. I at 2), and BRCAplus tests (*id.* at Exh. L at 3).

Defendant then compares the portions of the patient's genes that have been amplified and sequenced, including the sequence of all of the exonic portions of the BRCA1 and BRCA2 genes as deduced in the sequencing operation, to a wild-type or reference sequence that represents the commonly expected sequence for those genes. The reference sequence that Defendant uses is for the entire "human genome sequence," and thus it aligns all of the sequenced parts of the patient's genes—including the BRCA1 and BRCA2 genes—against the reference human genome sequence and compares the sequenced parts of the patient's genes to that entire reference sequence.[17] Using that comparison, Defendant locates "[a]ll identified variants," removes "variants that have been classified as benign," and performs "Mutation Detection."[18]

As additional steps in its BRCA1 and BRCA2 testing services, Defendant's large rearrangement analysis looks for large deletions and duplications of nucleotides. Depending on the test, Defendant uses either: 1) MLPA analysis for "comprehensive (full-gene) gross deletion/duplication analysis"; or 2) microarray analysis to "detect large rearrangement" and identify "gross deletions or duplications in all" genes analyzed.[19] Defendant uses MLPA as part of its BRCA1 and BRCA2 test.[20] Defendant uses microarray analysis as part of all of its "panel

[17] Elliott Decl. at ¶¶ 33-34; Defendant's NGS Cancer Panels PowerPoint (Dkt. 10 at Exh. B at 4); Defendant's Data Sheet for BRCA1/BRCA2 Test (*id*. at Exh. I) at 2; Roa Decl. at ¶¶ 27-28.

[18] Elliott Decl. at ¶¶ 33-34; Defendant's NGS Cancer Panels PowerPoint (Dkt. 10 at Exh. B at 4).

[19] Elliott Decl. at ¶¶ 42-50; Defendant's Data Sheet for BRCA1/BRCA2 Test (Dkt. 10 at Exh. I at 2); Defendant's Data Sheets for BRCAplus (*id*. Exh. L at 3); BreastNext (*id*. Exh. D at 5), CancerNext (*id*. at Exh. E at 6); and OvaNext tests (*id*. at Exh. F at 6).

[20] Elliott Decl. at ¶¶ 42-49; Defendant's Data Sheet for BRCA1/BRCA2 Test (Dkt. 10 at Exh. I at 2).

tests" that analyze the BRCA1 and BRCA2 genes, including at least its BRCAplus, BreastNext, CancerNext, and OvaNext tests.[21]

Defendant's MLPA and microarray processes use BRCA1- and BRCA2-specific probes. Specifically, Defendant's MLPA and microarray processes use "probes targeting the exons or flanking intronic sequences" in the BRCA1 and BRCA2 genes. The probes are complementary to, and thus hybridize to their respective target section if that section is present and has the same nucleotide sequence. Defendant's probes are specifically targeted for "the wild-type BRCA genes," and thus are specific for the wild-type alleles.[22]

In both the MLPA and microarray processes, Defendant's BRCA1- and BRCA 2-specific probes are allowed to hybridize to both (1) the synthetic DNA amplicons created from a patient's sample DNA and (2) the 'normal' wild-type reference DNA. Elliott Decl. at ¶¶ 43-48, 50-53; Elliott 2nd Decl. at ¶¶ 12-13; Roa Decl. at ¶¶ 31-37.

In Defendant's MLPA process, the probes that hybridize to adjacent genomic and wild-type reference sequences are ligated. The polymerase chain reaction process is then applied, amplifying each targeted part of the gene where hybridization of the probes has occurred. If a target section of the gene is present, then the probes hybridize, and the hybridization is detected because the PCR process creates many synthetic DNA molecules having the sequence of the

[21] Elliott Decl. at ¶¶ 42, 50; Defendant's Data Sheets for BRCAplus (Dkt. 10 at Exh. L at 3); BreastNext (*id*. at Exh. D at 5); CancerNext (*id*. at Exh. E at 6); and OvaNext tests (*id*. at Exh. F at 6).

[22] Elliott Decl. at ¶¶ 43, 47-52; MLPA – an introduction (MRC Holland) (Dkt. 10 at Exh. P) at 1-2; *see* Roa Decl. at ¶¶ 31-32, 35-37. As previously noted, "allele" refers to a form of the gene having a certain sequence, such as variant sequences or mutation sequences of interest and thus may be called a "wild-type allele" or a "mutated allele." Roa Decl. at ¶ 31.

target section for that probe. If a target section is not present, then the probes for that section do not hybridize to anything, and the fact that the target section is missing will be evident from the relative lack of synthetic DNA molecules corresponding to that section made during the PCR process. Elliott Decl. at ¶¶ 43-48; *see* Roa Decl. at ¶¶ 31-34. The resulting data allows Defendant to compare the patient's germline sequence to a wild-type sequence. Elliott Decl. at ¶¶ 46-48; Roa Decl. at ¶ 34. The data resulting from Defendant's microarray analysis identify both the existence of the allele and the existence of large base pair mutations in a germline nucleic acid sequence by comparing that sequence to the wild-type allele. Elliott Decl. at ¶¶ 50-53; *see id.* at ¶¶ 43-48; *see* Roa Decl. at ¶¶ 35-37.

G. The Patent Claims at Issue in Plaintiffs' Motions for Preliminary Injunction

In July 2013, Plaintiffs moved for a preliminary injunction seeking to prohibit Defendant from selling testing services based on alleged infringement of Myriad's patents. In their Motion for Preliminary Injunction, Plaintiffs allege that they are likely to prove that Defendant is infringing:

1) claims 16 and 17 of the '282 Patent;
2) claims 29 and 30 of the '492 Patent;
3) claims 7 and 8 of the '441 Patent;
4) claim 4 of the '857 Patent;
5) claim 5 of the '721 Patent; and
6) claims 2 and 4 of the '155 Patent.

(Dkt. 5 at 15-30.)

The allegedly infringed claims may be divided into two general categories. The first covers claims drawn to compositions of matter, and are collectively referred to as the Primer

Claims. These Primer Claims include claims 16 and 17 of the ’282 Patent, and claims 29 and 30 of the ’492 Patent. The remaining claims cover testing processes relating to BRCA1 and BRCA2, and the court collectively refers to them as the Method Claims. Each of the Method Claims is drawn to the mental process of comparing a genomic DNA sample to a DNA sequence that may be found in the BRCA1 and BRCA2 genes.

1. The Primer Claims

Claim 16 of the ’282 Patent provides:

> 16. A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction the sequence of said primers being derived from human chromosome 17q wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene.

Claim 17 of the ’282 Patent provides:

> 17. The pair of primers of claim 16 wherein said BRCA1 gene has the nucleotide sequence set forth in SEQ ID NO:1.

The term “SEQ ID NO:1” refers to the nucleotide sequence of the BRCA1 cDNA—the exon-only nucleotide sequence of the BRCA1 gene—as depicted in the Sequence Listing of the ’473 Patent, the ’282 Patent, and the ’999 Patent. ’473 Patent col.52 ll.50-56; ’282 Patent col.53 11.4-9; and ’999 Patent col.53 ll.16-22; Kay Decl. from *AMP* Litigation at ¶ 49 (Dkt. 34-4).

Claim 29 of the ’282 Patent provides:

> 29. A pair of single-stranded DNA primers of at least 15 nucleotides in length for determination of the nucleotide sequence of a BRCA2 gene by a polymerase chain reaction, the sequence of said primers being isolated from human chromosome 13, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA comprising all or at least 15 contiguous nucleotides of the BRCA2 gene.

Claim 30 of the ’282 Patent provides:

> 30. The pair of primers of claim 29 wherein said BRCA2 gene has the nucleotide sequence set forth in SEQ ID NO:1.

In the context of the BRCA2 patents, the term "SEQ ID NO:1" refers to the nucleotide sequence of the BRCA2 cDNA—the exon-only sequence—as depicted in the Sequence Listing of the '492 Patent. '492 Patent col.44 l.53—col.45 l.10; Kay Decl. from *AMP* Litigation at ¶ 50.

2. The Method Claims

a. Claims 7 and 8 of the '441 Patent

Claims 7 and 8 of the '441 Patent depend on claim 1, which is set forth below. The Federal Circuit held in the *AMP* litigation that claim 1 is drawn to patent ineligible subject matter—mental processes of comparing. The patent ineligible claim 1 recites:

> 1. A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject.

Claim 7 of the '441 Patent is drawn to the method of the patent ineligible claim 1, but

specifically requires the use of probes:[23]

> 7. The method of claim 1 wherein a germline nucleic acid sequence is compared by hybridizing a BRCA1 gene probe which specifically hybridizes to a BRCA1 allele to genomic DNA isolated from said sample and detecting the presence of a hybridization product wherein a presence of said product indicates the presence of said allele in the subject.

Claim 8 is drawn to the method of claim 1, but more specifically with the use of primers:

"The method of claim 1 wherein a germline nucleic acid sequence is compared by amplifying all

[23] At column 21, lines 35-50, the specification of the '441 Patent defines "probes" used in detecting BRCA1 alleles which predispose to certain cancers as being specific for those alleles:

> "Probes". Polynucleotide polymorphisms associated with BRCA1 alleles which predispose to certain cancers or are associated with most cancers are detected by hybridization with a polynucleotide probe which forms a stable hybrid with that of the target sequence, under stringent to moderately stringent hybridization and wash conditions. If it is expected that the probes will be perfectly complementary to the target sequence, stringent conditions will be used. Hybridization stringency may be lessened if some mismatching is expected, for example, if variants are expected with the result that the probe will not be completely complementary. Conditions are chosen which rule out nonspecific/adventitious bindings, that is, which minimize noise. Since such indications identify neutral DNA polymorphisms as well as mutations, these indications need further analysis to demonstrate detection of a BRCA1 susceptibility allele.

At column 15, lines 29-43, the specification of the '441 Patent teaches that probes used to identify mutations are "allele-specific," that is, are specific for a particular mutation:

> DNA sequences of the BRCA1 gene which have been amplified by screened [sic] using allele-specific probes. These probes are nucleic acid oligomers, each of which contains a region of the BRCA1 gene sequence harboring a known mutation. For example, one oligomer may be about 30 nucleotides in length, corresponding to a portion of the BRCA1 gene sequence. By use of a battery of such allele-specific probes, PCR amplification products can be screened to identify the presence of a previously identified mutation in the BRCA1 gene. Hybridization of allele-specific probes with amplified BRCA1 sequences can be performed, for example, on a nylon filter. Hybridization to a particular probe under stringent hybridization conditions indicates the presence of the same mutation in the tumor tissue as in the allele-specific probe.

or part of a BRCA1 gene from said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids."

b. Claim 4 of the '857 Patent

The Federal Circuit concluded in its *AMP* decision that claim 2 of the '857 Patent, on which claim 4 depends, is drawn to patent ineligible subject matter—abstract mental processes. Claim 2 provides:

> 2. A method for diagnosing a predisposition for breast cancer in a human subject which comprises comparing the germline sequence of the BRCA2 gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type BRCA2 gene or the sequence of its mRNA, wherein an alteration in the germline sequence of the BRCA2 gene or the sequence of its mRNA of the subject indicates a predisposition to said cancer.

Claim 4 of the '857 Patent recites the method of claim 2, but adds the use of an assay:

> 4. The method of claim 2 wherein the detection in the alteration in the germline sequence is determined by an assay selected from the group consisting of (a) observing shifts in electrophoretic mobility of single-stranded DNA on non-denaturing polyacrylamide gels, (b) hybridizing a BRCA2 gene probe to genomic DNA isolated from said tissue sample, (c) hybridizing an allele-specific probe to genomic DNA of the tissue sample, (d) amplifying all or part of the BRCA2 gene from said tissue sample to produce an amplified sequence and sequencing the amplified sequence, (e) amplifying all or part of the BRCA2 gene from said tissue sample using primers for a specific BRCA2 mutant allele, (f) molecularly cloning all or part of the BRCA2 gene from said tissue sample to produce a cloned sequence and sequencing the cloned sequence, (g) identifying a mismatch between (1) a BRCA2 gene or a BRCA2 mRNA isolated from said tissue sample, and (2) a nucleic acid probe complementary to the human wild-type BRCA2 gene sequence, when molecules (1) and (2) are hybridized to each other to form a duplex, (h) amplification of BRCA2 gene sequences in said tissue sample and hybridization of the amplified sequences to nucleic acid probes which comprise wild-type BRCA2 gene sequences, (i) amplification of BRCA2 gene sequences in said tissue sample and hybridization of the amplified sequences to nucleic acid probes which comprise mutant BRCA2 gene sequences, (j) screening for a deletion mutation in said tissue sample, (k) screening for a point mutation in said tissue sample, (l) screening for an insertion mutation in said tissue sample, (m) in situ hybridization of the BRCA2 gene of said tissue sample with nucleic acid probes which comprise the BRCA2 gene.

c. Claim 5 of the ’721 Patent

Claim 5 of the ’721 Patent depends on claim 1, which recites:

> 5. A method for determining an omi haplotype of a human BRCA1 gene comprising:
>
> (a) determining the nucleotide sequence of the BRCA1 gene or fragment thereof from at least one female individual with a family history which indicates a predisposition to breast cancer,
>
> (b) comparing the determined nucleotide sequence from said female individual to SEQ ID NO: 263,[24] and
>
> (c) determining the presence of the following nucleotide variations: thymine at nucleotides 2201 and 2731, cytosine at nucleotides 2430 and 4427, and guanine at nucleotides 3232, 3667 and 4956, wherein the presence of the nucleotide variations in the determined nucleotide sequence indicates the omi1 haplotype.

Claim 5 of the ’721 Patent recites, “The method of claim 1 wherein the BRCA1 gene or fragment thereof is amplified prior to nucleotide sequencing.”

d. Claims 2 and 4 of the ’155 Patent

Claim 2 of the ’155 Patent recites:

> 2. A method of identifying individuals having a BRCA1 gene with a BRCA1 coding sequence not associated with breast or ovarian cancer comprising:
>
> a) amplifying a DNA fragment of an individual’s BRCA1 coding sequence using an oligonucleotide primer which specifically hybridizes to sequences within the gene; b) sequencing said amplified fragment by dideoxy sequencing; c) repeating steps (a) and (b) until said individual’s BRCA1 coding sequence is completely sequenced; d) comparing the sequence of said amplified DNA to the sequence of SEQ. ID. NO: 1; e) determining the presence or absence of each of the following polymorphic variations in said individual’s BRCA1 coding sequence:
>
> AGC and AGT at position 2201,
>
> TTG and CTG at position 2430, CCG and CTG at position 2731,

[24] “SEQ ID NO:263” in claim 1 of the ’721 Patent refers to a contiguous cDNA sequence of all of the exons of BRCA1. *See* ’721 Patent cols.109-121; Pls.’ Reply Br. at 62-63.

GAA and GGA at position 3232,

AAA and AGA at position 3667,

TCT and TCC at position 4427, and AGT and GGT at position 4956; f) determining any sequence differences between said individual's BRCA1 coding sequences and SEQ. ID. NO: 1 wherein the presence of any of the said polymorphic variations and the absence of a polymorphism outside of positions 2201, 2430, 2731, 3232, 3667, 4427, and 4956, is correlated with an absence of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in the BRCA1 coding sequence.

Claim 4 of the '155 Patent recites:

4. A method of detecting an increased genetic susceptibility to breast and ovarian cancer in an individual resulting from the presence of a mutation in the BRCA1 coding sequence, comprising:

a) amplifying a DNA fragment of an individual's BRCA1 coding sequence using an oligonucleotide primer which specifically hybridizes to sequences within the gene;

b) sequencing said amplified fragment by dideoxy sequencing;

c) repeating steps (a) and (b) until said individual's BRCA1 coding sequence is completely sequenced;

d) comparing the sequence of said amplified DNA to the sequence of SEQ. ID. NO: 1;

e) determining any sequence differences between said individual's BRCA1 coding sequences and SEQ. ID. NO: 1 to determine the presence or absence of polymorphisms in said individual's BRCA coding sequences wherein a polymorphism which is not any of the following: AGC or AGT at position 2201, TTG or CTG at position 2430, CCG or CTG at position 2731, GAA or GGA at position 3232, AAA or AGA at position 3667, TCT or TCC at position 4427, and AGT or GGT at position 4956;

is correlated with the potential of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in the BRCA1 coding sequence.

"SEQ ID NO:1" recited in claims 2 and 4 of the '155 Patent is a contiguous cDNA sequence of all of the exons of BRCA1. '155 Patent col.19 ("Molecule Type: cDNA"); Pls.' Reply Br. at 62-63.

II. DISCUSSION

A. Preliminary Injunction Standards

The court "may grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable." 35 U.S.C. § 283. The Federal Circuit cautions, however, that "[a] preliminary injunction is a 'drastic and extraordinary remedy that is not to be routinely granted.'" *National Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1324 (Fed. Cir. 2004) (quoting *Intel. Corp. v. ULSI Sys. Tech., Inc.*, 995 F.2d 1566, 1568 (Fed. Cir. 1993)).

To obtain this extraordinary remedy, Plaintiffs must show four factors:[25]

> A plaintiff seeking a preliminary injunction must establish that [it] is likely to succeed on the merits, that [it] is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in [its] favor,[26] and that an injunction is in the public interest.

AstraZeneca, L.P. v. Apotex, Inc., 633 F.3d 1042, 1049 (Fed. Cir. 2010) (rehearing denied en banc *Jan.* 31, 2011) (quoting *Winter v. Natural Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008)); *see also Aria Diagnostics v. Sequenom, Inc.*, 726 F.3d 1296, 1304 (Fed. Cir. 2013) (noting that district court "correctly held that in addition to showing the likelihood of success on the merits,

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[25] The parties disagree about whether Federal Circuit or Tenth Circuit preliminary injunction standards apply to the preliminary injunction analysis in this case, with Defendant arguing that the regional circuit standards apply. The Federal Circuit has clearly stated that "a preliminary injunction enjoining patent infringement pursuant to 35 U.S.C. § 283 'involves substantive matters unique to patent law and, therefore, is governed by the law of this court.'" *Revision Military, Inc. v. Balboa Mfg. Co.*, 700 F.3d 524, 525 (Fed. Cir. 2012) (quoting *Hybritech Inc. v. Abbott Labs*, 849 F.2d 1446, 1451, n.12 (Fed. Cir. 1988)). Since the "issuance of an injunction pursuant to this section enjoins the violation of any right secured by patent . . . a preliminary injunction of this type, although a procedural matter, involves substantive matters unique to patent law and, therefore, is governed by the law of this court." *Id.* (quoting *Hybritech*, 849 F.2d at 525) (other citations omitted). The court applies Federal Circuit law here.

[26] This factor is often discussed in terms of the balance of the parties' comparative hardships. *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1344 (Fed. Cir. 2008) (citations omitted).

[the patent holder] must show it will likely suffer irreparable harm, that the balance of equities tips in its favor, and that an injunction is in the public interest.") (citing *Winter*, 555 U.S. at 20)).

Plaintiffs' showing on the first two factors is critically important. The Federal Circuit states that its "case law and logic both require that a movant cannot be granted a preliminary injunction unless it establishes *both* of the first two factors, i.e., likelihood of success on the merits and irreparable harm." *Amazon.com, Inc. v. Barnesandnoble.com*, 239 F.3d 1343, 1350 (Fed. Cir. 2001) (emphasis in original) (citations omitted) (vacating preliminary injunction and remanding where defendant raised substantial question of validity). Accordingly, the court focuses its analysis primarily on these two critical factors.

As discussed below, the court concludes that Plaintiffs have established that they are likely to suffer irreparable harm if an injunction does not issue. They have not, however, established that they are likely to succeed on the merits. Defendant has raised substantial questions concerning whether Plaintiffs' patents claim patent eligible subject matter. Further, the court finds that the harm Defendant will likely incur if an injunction issues outweighs the harm Plaintiffs are likely to suffer without an injunction, and that the public interest does not clearly favor an injunction. For these reasons, the court denies Plaintiffs' Motion for a Preliminary Injunction.

B. Irreparable Harm

Plaintiffs must demonstrate irreparable harm before an injunction may issue. This "entails showing a likelihood of substantial and immediate irreparable injury." *Apple Inc. v. Samsung Electronics Co., Ltd.*, 695 F.3d 1370, 1374 (Fed. Cir. 2012) (citations omitted). Irreparable injury may include "different types of losses that are often difficult to quantify, including lost sales and erosion in reputation and brand distinction." *Douglas Dynamics, LLC v.*

Buyers Prod. Co., 717 F.3d 1336, 1344 (Fed. Cir. 2013). "Price erosion, loss of goodwill, damage to reputation, and loss of business opportunities are all valid grounds for finding irreparable harm." *Aria Diagnostics*, 726 F.3d at 1304 (citations omitted).

The Federal Circuit cautions courts not to assume that a showing of irreparable harm is inadequate merely because patentees may eventually recover economic damages for infringement. That assumption strips patents of "their character as an exclusive right as articulated by the Constitution" and causes them to "become at best a judicially imposed and monitored compulsory license." *Id.* at 1304. Further, loss of market share can constitute irreparable harm even if it only moderately affects a patentee company's profitability or a small part of a company's business. *Robert Bosch, LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1152 (Fed. Cir. 2011) (quoting *Hoffman-LaRoche, Inc. v. Cobalt Pharm. Inc.*, 2010 WL 4687839, at *12 (D.N.J. Nov. 10, 2010) (a patentee's "size and profitability, and the small impact the likely harms would have on [its] overall profitability . . . says nothing about whether such harms are irreparable.")).

In this case, Plaintiffs claim that if Defendant is allowed to continue marketing the allegedly infringing tests, they are likely to be irreparably harmed in at least four ways:

1) through price erosion for Myriad's testing products, causing Myriad to lose the benefit of its established pricing strategy;
2) by reducing Myriad's testing product market share;
3) reputational injury to Myriad because the public will mistakenly associate flawed test results from the Defendant's testing with Myriad's allegedly superior testing products, resulting in dilution of Myriad's brand; and

4) by simply losing the benefit of the remainder of Myriad's patent terms, including Plaintiffs' right to exclude competitors, particularly where some of the patents at issue will begin to expire in August 2014.

The court discusses these alleged harms in turn.

1. Price Erosion and Loss of Market Share

For seventeen years, Myriad was the only company in the United States offering a full sequence test for the BRCA1 and BRCA2 genes. Ford Decl. at ¶ 8. That changed in June 2013, when Defendant began offering a multi-gene panel test for BRCA1 and BRCA2 at $2,200, significantly below Myriad's $4,040 integrated BRACAnalysis test (including BART). Ford Decl. at ¶ 11; Def's. Opp. Memo. at 15, ¶ 46.

Plaintiffs and their economist expert, Dr. James R. Kearl, claim that Plaintiffs are likely to suffer irreparable harm absent an injunction because Myriad is likely to lose its share of the BRCA1 and BRCA2 testing market—a market it previously monopolized in the United States. Plaintiffs contend that those seeking Defendant's lower priced testing likely represent lost Myriad customers. Further, Plaintiffs allege that Myriad faces a substantial threat of losing its third-party payor customers unless it lowers prices, thus leading to erosion of its pricing structure. Simply put, in a BRCA testing market where Myriad had been the lone seller, the

introduction of new competitors offering alternative testing will force Myriad to choose between lowering its price or losing customers. [27]

Defendant, relying on its CPA expert, Scott Hampton, offers a number of arguments in response. First, Defendant points out that Myriad has never before dropped its testing prices in response to public pressure, and suggests that this pricing stubbornness shows that Myriad will not now lower its prices, even in the face of competition. Hampton Decl. at ¶ 23. The court finds this entirely unpersuasive. That Myriad did not respond to public pressure says nothing about Myriad's response to new competitors entering its previously exclusive market with competing, lower-priced testing products. It is clear that pressure on Myriad to lower prices will be more acute and more effective than when customers had no market alternative. Regardless, if Myriad does not submit to that pressure to lower prices, it will undoubtedly lose market share. Kearl Decl. at 3, 7, 16-18.

Second, Defendant contends that the BRCA testing market is largely controlled by decision makers within third-party payors, such as insurers and health maintenance organizations. These third-party payors decide whether to pay for or reimburse testing costs. Defendant points out that Myriad has fixed long-term pricing agreements with many of these third-party payors. Thus, Defendant claims, Myriad will not need to lower its prices anytime soon. Hampton 2nd Decl. at ¶ 6 (Dkt. 134). Defendant also argues Plaintiffs have yet to identify

[27] There is an inverse relationship between the potential for price erosion and loss of market share. As Dr. Kearl explains, "to the degree that Myriad lowers its price in response to competition" from other testing companies, the price differences between Myriad and those companies "will be less, and the Myriad [market] share loss will also be less. However, in this case, while market share losses will be smaller, price erosion losses will be higher." Kearl Decl. at 17, n.19.

any third-party payor that has cancelled an agreement or successfully re-negotiated an existing long-term contract to obtain a lower testing price.

But Defendant fails to recognize that Myriad permits those third-party payors to cancel their long-term contracts with 90 days' notice to Myriad. Sept. 12, 2013 Hearing Tr. (Ford) at 314:18-24. Moreover, Plaintiffs recently submitted evidence that at least one third-party payor, the Centers for Medicare and Medicaid Services (CMS), has decided to lower its reimbursement rate for BRCA1 and BRCA2 testing from $2,700 to $1,438.14. (Dkt. 177-1.)[28] The evidence before the court shows that Myriad is clearly experiencing pressure from third-party payors to reduce prices. Ford Decl. at ¶ 16. Notwithstanding that CMS is the lone third-party payor identified by Plaintiffs as lowering reimbursement rates, and that Plaintiffs have thus far avoided any other renegotiated or cancelled contracts, Plaintiffs have shown that it is only a matter of time before the pricing pressure from Defendant's testing causes renegotiated or cancelled contracts. Without an injunction, it is clear that Myriad will have to either lower its testing price or lose market share—or possibly both.

Third, Defendant contends that an injunction is unnecessary even if market forces cause Myriad to reduce its prices because Myriad will be able to raise prices again if Plaintiffs ultimately prevail in this lawsuit on the merits. Hampton Decl. at ¶ 25. But Dr. Kearl persuasively notes that once prices drop, Myriad will face daunting resistance to reinstating higher prices. Kearl Decl. at 11-13; *see also Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1382 (Fed. Cir. 2006) (*reh'g and reh'g en banc* denied Jan. 19, 2007) (affirming entry of

[28] The court has taken judicial notice that CMS lowered its reimbursement rate on January 1, 2014. (Dkt. Nos. 177-1 and 181.) This rate remains subject to change following closure of a public comment period, originally slated for January 27, 2014, but which has been extended to February 28, 2014. *See id.;* and *Gapfill Pricing Inquiries,* <http:// www. cms.gov/ Medicare/ Medicare-Fee-for- Service-Payment/ClinicalLabFeeSched/Gapfill-Pricing-Inquiries.html>.

preliminary injunction for drug patentee; citing with approval district court's irreparable harm analysis which found that it would be nearly impossible to restore pre-competition pricing). The court finds Dr. Kearl's price-resistance analysis persuasive, particularly where Myriad's patents will begin to expire in August 2014, long before any resolution of this dispute on the merits. Kearl Decl. at 11-15; Ford Decl. at ¶ 21; *see also Pfizer, Inc. v. Teva Pharm., USA, Inc.*, 429 F.3d 1364, 1380 (Fed. Cir. 2005) (noting that district court properly concluded that accused drug patent infringer's sales of generic drug "would cause substantial harm to [the patentee] and loss of statutory right to exclude . . . for the [relatively short] remaining life of the . . . patent . . . .").

Fourth, Defendant appears to argue that Myriad has the financial capability to keep its pricing structure, even if it causes Myriad to lose money or market share. *See* Def's. Opp. Memo. at 89 (noting that Myriad's "$400 million in cash and cash equivalents will allow it to maintain its current pricing structure during the pendency of this suit if it chooses to do so."); Hampton Decl. at ¶ 66. Defendant also points out that Myriad has projected continued revenue growth for Fiscal Year 2014, despite competition from BRCA1 and BRCA2 testing companies. Hampton Decl. at ¶¶ 52-53. Based on these projections, Defendant contends that Myriad cannot seriously believe it will suffer irreparable injury, even if it experiences price erosion or loss of market share.

Defendant's argument fails to rebut Dr. Kearl's logical and persuasive testimony that Plaintiffs will suffer irreparable financial harm if an injunction does not issue. This harm need not destroy Myriad in order to be irreparable. The Federal Circuit has explained that a loss of market share can constitute irreparable harm even if it only moderately affects profitability or a portion of a patentee's business. *Robert Bosch*, 659 F.3d at 1152 (the "fact that an infringer's harm affects only a portion of a patentee's business says nothing about whether that harm can be

rectified.") (citing *Hoffman-LaRoche, Inc.*, 2010 WL 4687839, at *12 (rejecting notion that harm is not irreparable if patentee is large and profitable, and infringement allegedly has "small impact . . . on . . . overall profitability.")). That Myriad continues to project overall profitability does not "automatically rebut a case for irreparable injury." *Douglas Dynamics*, 717 F.3d at 1344 (rejecting district court's reasoning that permanent injunction should not issue where patentee snow plow company's market share increased by one percent per year after accused infringer introduced its competing snow plow assembly; noting market share might increase for various reasons unrelated to the infringing conduct).

Finally, Defendant contends that its entry into the BRCA testing market has actually expanded that market, particularly for those who seek less expensive tests and "meaningful second opinion testing." Def's. Opp. Memo. at 95. Defendant argues Myriad cannot be harmed "by the loss of sales it never would have realized." *Id*. at 96. Defendant does not contend that complete mutual exclusivity exists between potential Myriad customers, whether third-party payors or individuals, and those who will seek out Defendant's less expensive tests during the remainder of Myriad's patent terms. It defies reason to conclude that Defendant's customers will comprise only persons who could not have obtained via direct payment or a third-party payor a higher-priced Myriad BRCA1 and BRCA2 test. Nor does the record in any way support such a finding.

The court concludes that Plaintiffs have adequately demonstrated they are likely to suffer irreparable harm in the form of price erosion and loss of market share if an injunction does not issue.

2. Reputational Harm

Plaintiffs also claim that their reputations will be irreparably diluted and damaged absent injunctive relief. *See Douglas Dynamics*, 717 F.3d at 1344-45 (harm to reputation can be irreparable harm). Plaintiffs contend that dilution will occur because Myriad was, until recently, the only BRCA testing provider in the United States, and thus medical providers and patients naturally associate this testing with Myriad. Pls.' Reply Br. at 136. Plaintiffs also contend that Defendant's entry into the market will damage their reputations, because Defendant's testing is less reliable and yields higher percentages of "variants of unknown significance" (VUS)—variants that are difficult to categorize as either harmful or benign. Plaintiffs are concerned that consumers will attribute flawed results with Myriad.

Plaintiffs assert that over 97 percent of those tested with Myriad's BRACAnalysis who receive a report identifying a genetic variation will be informed about the clinical significance of the variant. Ford Decl. at ¶¶ 6-7. In other words, Plaintiffs claim that Myriad's VUS rate is about 3 percent. Myriad submits this low rate is due to its ability to utilize its privately maintained database of genetic variant information, developed over many years and with $100 million in investment. *Id.* Plaintiffs contend that third-party payors who reimburse testing may be uninformed about the comparative high quality of Myriad's testing and might associate others' flawed test results with Myriad. Plaintiffs cite no survey, interviews, correspondence, or any other empirical evidence concerning consumer choice to support this claim directly.[29] Still, Plaintiffs claim that they cannot mitigate this alleged misperception without an injunction, which

[29] *See* Kearl Decl. at 19 ("… given the very short period of time that Defendants' [Ambry and dismissed Defendant, Gene by Gene] tests have been available, it is hardly surprising that evidence of *actual* confusion is lacking.").

would offer time to educate the public about the superiority of their testing—including the newly introduced myRisk test. Ford Decl. at ¶¶ 17, 21-23.

Plaintiffs' arguments here fall short. First, there is no competent evidence showing that Defendant's tests are meaningfully less accurate or reliable than Myriad's tests. Defendant compellingly points out that Myriad's VUS rate is based on data that Myriad does not share with the public and is difficult to verify. Defendant's current VUS rates are 4.2 percent. Chao Decl. at ¶¶ 52-53; Chao 2nd Decl. ¶ 2 (Dkt. 137).[30] These rates are already low and will go down over time. VUS rates are highest right after a test is first offered, but they decrease as more tests are run and more data becomes available to assist with classification. Swisher Decl. at ¶¶ 52-53; Chao Decl. at ¶ 52. Moreover, Plaintiffs simply provide no evidence of consumer confusion between testing companies.

But Plaintiffs insist they may suffer reputational harm if Defendant's entry into the BRCA testing market causes "dilution of Myriad's reputation," where Myriad was until recently "the only provider of genetic predisposition testing for breast and ovarian cancer . . . and thus providers and patients naturally associate the test with Myriad." Pls.' Reply Br. at 136. In *Douglas Dynamics*, the plaintiff snow plow company sought a permanent injunction against a competing snow plow company. 717 F.3d at 1338-39. The district court denied the injunction, stating there was no reputational harm because there was no customer confusion. *Id.* at 1344. The Federal Circuit disagreed, finding that reputational harm may result even without actual

[30] In their Reply Brief, Plaintiffs express skepticism about this rate but do not dispute it with any evidence. Geier Decl. at ¶ 29 (Dkt. 104) (noting that Defendant "is reportedly quoting a 5% VUS rate, but I don't believe that estimate has yet been validated since they have only been doing testing for a few weeks."). Defendant notes that while Plaintiffs question its VUS rate, it is actually more transparent in its VUS rate determination than Myriad is because Defendant provides full variant data information to patients, their doctors, and genetic counselors through test reports. Chao Decl. at ¶¶ 58-59, Exh. L; Swisher Decl. at ¶¶ 46-49, Exhs. G, I.

customer confusion. This was due to the possibility that consumers would see the patentee's innovations appearing in products "considered less prestigious and innovative," or that the patentee's dealers might believe it "did not enforce its intellectual property rights." *Id.*

In contrast, Plaintiffs here offer no clear evidence suggesting that the public would view Defendant's testing products as less prestigious or innovative. In fact, Myriad's newly launched myRisk test is a multi-gene panel test that utilizes Next Generation Sequencing—much like Defendant's multi-panel CancerNext test.[31] Plaintiffs' contention that their reputations will be besmirched by the continued sale of Defendant's testing products does not withstand scrutiny. At least at this preliminary stage, the court concludes that Plaintiffs have not shown that Defendant's testing is likely to cause irreparable harm to Plaintiffs' reputations.

3. Loss of Remainder of the Exclusive Patent Terms

Plaintiffs also contend that Defendant's alleged infringement deprives Plaintiffs of enjoyment of their patents' exclusive terms. Myriad says this causes irreparable harm because its long-term corporate strategy was based on an expectation that Plaintiffs would enjoy their exclusive patent terms until they began to expire in August 2014, giving Myriad time to develop and introduce to the public new products, including the recently released myRisk cancer test. *Robert Bosch*, 659 F.3d at 1149 (citing *Acumed LLC v. Stryker Corp.*, 551 F.3d 1323, 1328 (Fed. Cir. 2008) (in view of right to exclude, "infringement may cause a patentee irreparable harm not remediable by a reasonable royalty.")).

Defendant responds that because Myriad has not yet sued every company that is or has announced plans to begin BRCA1 and BRCA2 testing, Myriad has inconsistently enforced its patents. It claims that this demonstrated Plaintiffs' indifference to their patents' exclusive terms.

[31] Myriad launched myRisk on September 5, 2013.

But the Federal Circuit has observed that "[p]icking off one infringer at a time is not inconsistent with being irreparably harmed." *Robert Bosch, LLC,* 659 F.3d at 1151 (quoting *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 429 F.3d at 1381). Were the court to find otherwise, it would "effectively establish a presumption against irreparable harm whenever the market contains a plurality of players":

> Under such circumstances, the first infringer sued could always point to the existence of additional competitors. And, perversely, if that infringer were to succeed in defeating an injunction, subsequent adjudged infringers could point to the market presence of the first infringer when opposing a request for an injunction. Consequently, without additional facts showing that the presence of additional competitors renders the infringer's harm reparable, the absence of a two-supplier market does not weigh against a finding of irreparable harm.

Id. (noting that patent holder had "diligently pursued infringers"; reversing district court's finding that the "absence of a two-player market effectively prohibit[ed] a finding of irreparable harm."). Thus, even if Plaintiffs have not sued every company that has announced an intent to conduct BRCA1 and BRCA2 testing, this does not mean that Plaintiffs cannot show irreparable harm here.

Moreover, it appears that Plaintiffs have been diligent, and not indifferent, in enforcing their patents through litigation in the recent aftermath of the Supreme Court's decision in *AMP* just a few months ago. *See supra* note 3 (discussing current litigation involving Plaintiffs and alleged infringers). By all indications, Myriad and the other Plaintiffs are actively defending their patent exclusivity. The court finds that the Plaintiffs' claimed harm from the loss of exclusivity of Myriad's patent terms bolsters Plaintiffs' showing that they likely will suffer irreparable harm without injunctive relief.

4. Damages Calculation and Defendant's Ability to Pay

Defendant claims that even if Plaintiffs have shown a likelihood of harm, particularly through price erosion, this harm is compensable with money damages, rendering a preliminary injunction unwarranted. Defendant relies on its CPA expert, Scott Hampton, who states that because "Myriad enjoyed a near perfect monopoly prior to June of 2013," there will be a clean starting point from which to calculate Plaintiffs' damages. Hampton Decl. at ¶ 31. In considering this issue, the court must heed the clear instruction from the Federal Circuit to act with caution in assuming that money damages will suffice when Plaintiffs have shown harms likely flowing from price erosion, loss of market share, and loss of patent terms, as is the case here. *Aria Diagnostics,* 726 F.3d at 1304.

Plaintiffs maintain that unless an injunction issues, the complex pricing and sales factors in this case present a substantial danger that they will be undercompensated if they prevail on the merits. Kearl Decl. at 15. The court agrees.

First, Myriad does not charge one set price for every test, but instead may alter its pricing by test type, customer, and time period. Kearl Dec. at 8. It will be especially challenging here to determine, once all prices decline, the price that customers would have paid Myriad but for Defendant's entry into the market.

Second, Defendant appears to assume that if Plaintiffs eventually prevail, Myriad will be able to reverse the price erosion that will occur without an injunction. As explained above, the court agrees with Plaintiff's economist, Dr. Kearl, who concludes that this is unlikely. Kearl Decl. at 11-13.

Finally, in the aftermath of the Supreme Court's *AMP* decision, numerous companies are offering or planning to offer close substitute BRCA1 and BRCA2 testing. Although Myriad has

been seeking to stop the accused infringers through litigation, it will be very challenging for Plaintiffs to show the degree to which any accused infringer should be held responsible for price erosion. Or, if Myriad does not lower its pricing, it will be difficult to show which sales a competitor enjoys would otherwise have been Myriad's, and at what price. Kearl Decl. at 15-16. As Dr. Kearl states:

> When the damages estimation becomes more complex, the losses that are clearly the result of the specific challenged conduct of the specific defendant before the court become a smaller amount. In this way, complexity tends to lead—in practice—to lower economic damages estimates and awards, and under compensation of the plaintiff.

Id. at 18.

Moreover, the court is concerned with Defendant's ability to pay a large damage award if Plaintiffs prevail in this litigation. The Federal Circuit has found that an accused infringer's "lack of financial wherewithal to satisfy a judgment" may be considered in evaluating irreparable harm. *Robert Bosch*, 659 F.3d at 1151. Here, Defendant and its experts allege that Defendant will be forced to close its doors and terminate its 180 employees if a preliminary injunction is entered. This is due to substantial investments made to prepare to conduct BRCA1 and BRCA2 testing and the centrality of that testing to its revenue stream. Hampton Decl. at ¶ 57. This allegation raises serious concerns about Defendant's ability to satisfy a substantial damage award.

For these reasons, the court concludes that Plaintiffs have shown they are likely to suffer irreparable harm in the form of lost market share, price erosion, and loss of the remainder of their exclusive patent term if a preliminary injunction does not issue.

C. Likelihood of Success on the Merits

Before an injunction may issue, Plaintiffs must also demonstrate that they are likely to succeed on the merits of their asserted infringement claims. Plaintiffs argue that their Primer and Method Claims are drawn to patent eligible subject matter under 35 U.S.C. § 101. They further assert that their patents are valid and infringed by Defendant. Specifically, Plaintiffs claim they likely will succeed in proving infringement of ten claims: claims 16 and 17 of the '282 Patent; claims 29 and 30 of the '497 Patent; claims 7 and 8 of the '441 Patent; claim 4 of the '857 Patent; claim 5 of the '721 Patent; and claims 2 and 4 of the '155 Patent.

Defendant contends that Plaintiffs have failed to demonstrate a likelihood of success on the merits. Defendant argues that it has raised a substantial question about whether Plaintiffs' Primer and Method Claims are directed to products of nature or abstract ideas—subject matters ineligible for patent protection under 35 U.S.C. § 101. Second, Defendant argues the claims at issue are invalid because the Primer Claims are anticipated under § 102 and the Method Claims are obvious under § 103. Third, Defendant alleges that two of the Primer Claims, claim 17 in the '282 Patent and claim 30 of the '492 Patent, are invalid because of indefiniteness under § 112; and one Method Claim, claim 4 of the '155 Patent, fails because of inadequate written description under § 112. Finally, Defendant argues that Plaintiffs are not likely to succeed in proving that Defendant is infringing any of the ten claims at issue.

Below, the court analyzes as a threshold matter whether Plaintiffs' asserted Primer and Method claims are drawn to subject matter eligible for patent under § 101, and finds that Defendants have convincingly succeeded in raising a substantial question as concerning the subject matter eligibility of each of these claims. The court therefore concludes Plaintiffs have not met their burden to show a likelihood of success on the merits of their asserted infringement

claims. For this reason, the court does not reach the alternative bases offered by Defendant in opposition to Plaintiffs' likelihood of success arguments.

1. Burdens and the Presumption of Validity

To establish they are likely to succeed on the merits, Plaintiffs must show that they "will likely prove infringement of one or more claims of the patents-in-suit, and that at least one of those same allegedly infringed claims will also likely withstand the validity challenges presented by [Defendant]." *AstraZeneca*, 633 F.3d at 1050 (citations omitted). If Defendant raises "a substantial question" regarding infringement or validity—including patent subject matter eligibility—Plaintiffs cannot show a likelihood of success on the merits unless they demonstrate that the infringement or invalidity defense lacks substantial merit. *Id.* (citations omitted); *Aria Diagnostics*, 726 F.3d at 1304 (remanding for district court to consider infringement of patented claims to methods of detecting fetal genetic characteristics and validity challenges, including subject matter eligibility in light of *AMP*).

Under 35 U.S.C. § 282(a), patents are generally "presumed valid," even at the preliminary injunction stage. *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1377 (Fed. Cir. 2009) (citations omitted). This rebuttable presumption generally applies to subject matter eligibility challenges under 35 U.S.C. § 101 in addition to validity challenges under §§ 102 and 103, and description challenges asserted under § 112. *Ultramercial, Inc. v. Hulu, LLC*, 722 F.3d 1335, 1342 (Fed. Cir. 2013). The presumption is earned when the USPTO approves a

patent because the USPTO "rejects claims if they are drawn to ineligible subject matter, just as it rejects claims if not compliant with §§ 102, 103, or 112."[32] *Id.*

An accused infringer attacking a patent's validity at the preliminary injunction stage bears the burden to "come forward with evidence of invalidity, just as it would be at trial." *Titan Tire*, 566 F.3d at 1377. The patentee must then respond with contrary evidence to show a likelihood of success on the merits. *Id.* At this early stage, however, the court "does not resolve the validity question," but instead assesses "the persuasiveness of the challenger's evidence, recognizing that it is doing so without all the evidence that may come out at trial." *Id.* (citations omitted). In other words, the alleged infringer need not persuade the court that the patent is invalid. Rather, in seeking the extraordinary relief of a preliminary injunction, "it is the patentee, the movant, who must persuade the court that, despite the challenge presented to validity, the patentee nevertheless is likely to success at trial on the validity issue." *Id.*

With regard to the presumption of subject matter eligibility in the area of gene patents, the Supreme Court in *AMP* notably rejected Myriad's contention that the USPTO's "past practice of awarding gene patents is entitled to deference." 133 S. Ct. at 2118 (citations omitted). The Court pointed out that Congress had not endorsed with subsequent legislation the USPTO's practice in this area. *Id.* Further, in the *AMP* litigation, the United States had argued "that isolated DNA was *not* patent eligible under § 101," and that the USPTO's practice was not 'a sufficient reason to hold that isolated DNA is patent-eligible.'" *Id.* (emphasis in original)

[32] Myriad claims that because the *AMP* plaintiffs did not challenge every claim now asserted in this litigation, this "underscores the conclusion that they are valid and patentable, or, at an absolute minimum, that Myriad is more likely than not to establish this factor at trial on the merits." (Dkt. 5 at 14, n.5). The court disagrees that the claims the *AMP* plaintiffs chose to challenge in their suit constitute evidence of the validity of Plaintiffs' other claims in this case.

(quoting United States' Amicus Curiae Brief at 26). These circumstances "weigh[ed] against deferring to the PTO's determination." *Id.* On the same day the Supreme Court issued its *AMP* ruling, the USPTO delivered the following guidance to its own patent examiners:

> As of today, naturally occurring nucleic acids are not patent eligible merely because they have been isolated. Examiners should now reject product claims drawn solely to naturally occurring nucleic acids or fragments thereof, whether isolated or not, as being ineligible subject matter under 35 U.S.C. § 101. Claims clearly limited to non-naturally-occurring nucleic acids, such as a cDNA or a nucleic acid in which the order of the naturally occurring nucleotides has been altered (e.g., a man-made variant sequence), remain eligible. Other claims, including method claims, that involve naturally occurring nucleic acids may give rise to eligibility issues and should be examined under the existing guidance in MPEP 2106, Patent Subject Matter Eligibility.[33]

The court need not decide whether the Supreme Court's refusal in *AMP* to defer to the USPTO's past practice of awarding gene patents weakens the initial presumption of subject matter eligibility for Plaintiffs' patent claims. Even if the presumption applies, the court concludes that Defendant has persuasively come forward with evidence to overcome it.

2. Section 101 Patent Eligible Subject Matter

The Supreme Court characterizes the subject matter eligibility inquiry as a "threshold test." *Bilski*, 130 S. Ct. at 3225. Treating it as such in this case is particularly appropriate given the recent, closely related *AMP* litigation addressing the patent eligibility of several Myriad BRCA1 and BRCA2 patent claims. *Id.; see also Parker v. Flook*, 437 U.S. 584, 593 (U.S. 1978) (noting that "obligation to determine what type of discovery is sought to be patented must precede the determination of whether that discovery is, in fact, new or obvious.").

Under 35 U.S.C. § 101, "[w]hoever invents or discovers any new and useful [1] process, [2] machine, [3] manufacture or [4] composition of matter, or any new and useful improvement

[33] <http://www.uspto.gov/patents/law/exam/myriad_20130613.pdf> (emphasis in original).

thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." The first step in evaluating a patent's subject matter eligibility is to "identify whether the claimed invention fits within one of the four statutory classes set out in § 101." *Accenture Global Services, GmbH v. Guidewire Software, Inc.*, 728 F.3d 1336, 1341 (Fed. Cir. 2013) (citations omitted). The statute's broad language suggests Congress "contemplated that the patent laws would be given wide scope." *Chakrabarty*, 447 U.S. at 308.

But while claimed inventions may otherwise fall within § 101, important exceptions apply: "'[l]aws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo*, 132 S. Ct. at 1293 (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)) (other citations omitted). This is so irrespective of whether inventions are "[g]roundbreaking, innovative, or even brilliant," *AMP*, 133 S. Ct. at 2117, or "just discovered," because "they are the basic tools of scientific and technological work." *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972). Patents granted over these basic tools create "considerable danger" that their use would be "tie[d] up," thereby "inhibit[ing] future innovations premised upon them." *AMP*, 122 S. Ct. at 2116 (quoting *Mayo*, 132 S. Ct. at 1301). Such innovation-impeding monopolization is at odds with the "very point of patents, which exist to promote creation." *AMP*, 133 S. Ct. at 2116 (citing *Chakrabarty*, 447 U.S. at 309).

This is illustrated in *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), where the patentee discovered that certain strains of bacteria did not exert a mutually inhibitive effect on each other. The patentee created a mixed bacteria culture that could inoculate several species of leguminous plant seeds. This creation required ingenuity. Still, the Supreme Court concluded the discovery was patent ineligible because it was drawn to "the handiwork of nature," where each of the combined bacteria possessed the same utility it had before it was

combined to produce the new use. *Id.* at 131 (the combined bacteria "perform in their natural way," serving the "ends nature originally provided . . . .").

Patents drawn to processes focused on patent ineligible subject matter may likewise be patent ineligible, unless the processes include an "inventive concept" sufficient to "ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Mayo*, 132 S. Ct. at 1294. For example, applying *Mayo*, the Federal Circuit in *AMP* found five of Myriad's six challenged method claims patent ineligible because they were drawn to the abstract ideas of "analyzing" and "comparing" BRCA DNA sequences. *See* discussion of Federal Circuit *AMP* opinions *supra* Part I.E.2.

The Supreme Court cautions that these exceptions to § 101 should be applied with care, as "all inventions at some level embody, use, reflect, rest upon or apply laws of nature, natural phenomena, or abstract ideas." *Mayo*, 132 S. Ct. at 1293. In *Chakrabarty*, the Court found patent eligible a new, genetically engineered bacterium capable of breaking down crude oil—a utility "possessed by no naturally occurring bacteria." 447 U.S. at 305. The claim was "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity having a distinctive name, character [and] use." *Id.* at 309-10 (citations omitted). Unlike *Funk Bros.*' bacteria mixture, this was a "new bacterium with markedly different characteristics from any found in nature. . . ." *Id.* at 310.

The court analyzes Plaintiffs' asserted Primer and Method Claims in light of these principles. While the patent eligibility analysis is "ultimately a legal determination," it is one "rife with underlying factual issues." *Ultramercial*, 722 F.3d at 1339.

a. Section 101 Subject Matter Eligibility of the Primer Claims

Plaintiffs' four Primer Claims are drawn to pairs of single stranded primers for use in determining the nucleotide sequence of BRCA1 or BRCA2 genes. The two independent Primer Claims (claim 16 of the '282 Patent and claim 29 of the '492 Patent) are drawn to pairs of single stranded DNA primers for use in determining the sequence of either a BRCA1 or BRCA2 gene, where the primers' sequences are derived or isolated from chromosomes 17q (BRCA1) or 13 (BRCA2). The two dependent Primer Claims (claim 17 of the '282 and claim 30 of the '492 Patent) are drawn to primer pairs of the independent Primer Claims, but where the BRCA1 or BRCA2 gene "has the nucleotide sequence set forth in SEQ ID NO:1"—the exon-only sequence. The Primer Claims' nucleotide sequences complement BRCA1 and BRCA2 sequences found in nature.

Notwithstanding this, Plaintiffs argue that because their Primer Claims are drawn to synthetic DNA, their BRCA1 and BRCA2 primers are therefore patent eligible. Plaintiffs contend that the Supreme Court in *AMP* found only extracted, genomic DNA to be patent ineligible; but that cDNA was found patent eligible because it is synthetic. Plaintiffs further argue that the claimed primers are patent eligible because they are "markedly different" from naturally occurring DNA. Here, Plaintiffs rely on the facts that the primers: 1) are single stranded, matched pairs of DNA; 2) are shorter than an entire BRCA1 or BRCA2 gene; and 3) have unique utility—to prime PCR. The court addresses each of Plaintiffs' arguments in turn.

The court's analysis of Plaintiffs' arguments necessarily begins with a careful review of the *AMP* litigation. As discussed below, the *AMP* Supreme Court ruled that isolated DNA segments were patent ineligible as long as they reflected naturally occurring BRCA1 and BRCA2 sequences. This decision, when understood in light of the lower court decisions and the

arguments advanced by Myriad in the *AMP* litigation, excludes from patent eligibility synthetic DNA that reflects naturally occurring BRCA1 and BRCA2 sequences. At every step, the *AMP* courts understood the isolated DNA at issue included both extracted genomic DNA and synthetic DNA. Thus, as described below, the court rejects Plaintiffs' argument that their Primer Claims are patent eligible because those claims relate to synthetic DNA.

But even if the court could conclude that the Supreme Court's *AMP* decision is not dispositive of the issue, the court independently reads the relevant authority—including the decisions in *AMP*, *Chakrabarty*, and *Funk Bros.* to compel the same conclusion, that Plaintiffs' Primer Claims are drawn to patent ineligible products of nature.

i. Under *AMP*, Synthetic DNA May be Patent Ineligible if it Reflects the Same Nucleotide Sequence as Naturally Occurring DNA

The *AMP* district court and the Federal Circuit panel understood that case to present squarely the issue of the patent eligibility of isolated DNA, including primers and probes. The *AMP* district court construed "isolated DNA" as Myriad urged, to "refer to a segment of DNA nucleotides existing separate from other cellular components normally associated with native DNA, including proteins and other DNA sequences comprising the remainder of the genome, and includes both DNA originating from the cell as well as DNA synthesized through chemical or heterologous biological means." 702 F. Supp. 2d at 217; '282 Patent col.19 11.8-18; and '492 Patent col.17 ll.62—col.18 l.5. Judge Sweet noted that Myriad argued "native and isolated DNA" had "markedly different" functions because "isolated DNA may be used in applications for which native DNA is unsuitable, namely, in molecular diagnostic tests (e.g., *as probes, primers*, templates for sequencing reactions) . . . ." *Id.* at 230 (citations to Myriad's briefing omitted) (emphasis added). Judge Sweet nevertheless found all isolated DNA patent ineligible, as it is not "markedly different" from native, genomic DNA.

Likewise, the three Federal Circuit Judges on the *AMP* panel ruled on the patent eligibility of "isolated DNA," which they understood to include primers and probes. As it had below, Myriad again argued to the Federal Circuit that "isolated DNAs, unlike native DNAs, can be used as primers and probes for diagnosing cancer." 689 F.3d at 1325. Judge Lourie explained that "isolated DNA" is DNA that has been "cleaved . . . or synthesized to consist of just a fraction of a naturally occurring DNA molecule." *Id.* at 1328. Judge Moore observed that the "smaller isolated DNA sequences" have "a variety of applications and uses in isolation that are new and distinct as compared to the sequence as it is in nature . . . [T]hese sequences can be used as *primers . . . [and] probes* . . . ." *Id.* at 1341 (emphasis added). Judge Bryson did not explicitly use the term "primer" in relation to the non-cDNA isolated DNA. But his stated rationale for finding non-cDNA isolated DNA patent ineligible applies equally to DNA synthetically created for use as a primer as well as to extracted, genomic DNA. He noted that while isolated DNA molecules have been cleaved and have "terminal groups that differ from those found on naturally occurring genes," they have the same sequence, code for the same proteins, and represent the same units of heredity. *Id.* at 1352. Their function is "dictated by the nucleotide sequence of the gene—a sequence that is determined by nature and that appears in nature exactly as it appears in the claimed isolated DNA." *Id.*

Like Judge Bryson, the Supreme Court in *AMP* does not explicitly use the terms "primer" or "probe" when discussing the non-cDNA claims before it. Instead, the Court held that "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but that cDNA is patent eligible because it is not naturally occurring." 133 S. Ct. at 2111. In conclusion, the Court stated: "We merely hold that genes and the information

they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material." *Id.* at 2120.

In contrast to Myriad's (successfully) urged definition of "isolated DNA" throughout the *AMP* litigation, Plaintiffs now reverse course and argue that the isolated DNA the *AMP* Court found patent ineligible was only genomic DNA that is extracted from its natural environment, not synthetic DNA such as primers and probes. Pls.' Reply Br. at 40 (the Court "used the term 'isolation' only to mean 'extraction' of genomic DNA."). Springing from this interpretation, Plaintiffs suggest that if the Court found patent ineligible only isolated—now viewed by Plaintiffs to mean only genomic, extracted DNA—then the Court must have in a blanket fashion "affirmed the patent eligibility of synthetic DNA," finding that "unlike isolated human genes, synthetic DNA is man-made and not a product of nature." Pls.' Mot. for Prel. Inj. at 4. Thus, Plaintiffs argue that "the very framework that the Court used—the distinction between naturally occurring DNA (which it held unpatentable) and artificially created, synthetic DNA, along with the methods of applying knowledge about the genes—leads to the conclusion that the claims Myriad asserts here, all of which fall into the latter category, are valid and enforceable." (*Id.* at 14.)

Plaintiffs further contend the Federal Circuit utilized Plaintiffs' now-urged 'isolated DNA as distinct from synthetic DNA' analysis. Plaintiffs claim that when the Federal Circuit heard the *AMP* case on remand, it held "that both isolated DNA and synthetic DNA were patent eligible under § 101, noting that 'each of the claimed molecules represents a non-naturally occurring composition of matter.'" Pls.' Mot. for Prel. Inj. at 7, n.1 (quoting Federal Circuit's *AMP* decision, 689 F.3d at 1309).

Plaintiffs fail to recognize the Federal Circuit separately analyzed 'isolated DNA' and cDNA, and noted that both these categories of DNA encompassed synthetic DNA. Judge Lourie pronounced: "[t]he isolated DNA molecules before us are not found in nature. They are obtained in the laboratory and are man-made, the product of human ingenuity." 689 F.3d at 1325. That was precisely as Myriad argued before that court, stating in its briefing that "isolated DNA does not exist in nature and that isolated DNAs, unlike native DNAs, can be used as primers and probes for diagnosing cancer." *Id.* [34]

The distinction Plaintiffs now urge between extracted, genomic DNA on the one hand, and synthetic DNA on the other hand, does not withstand a close reading of *AMP*—even setting aside Myriad's directly contrary arguments in the *AMP* litigation and Judge Sweet's unchallenged claim construction.

First, the only synthetic DNA the *AMP* Court expressly found patent eligible was cDNA. Even then, the Court held only that cDNA may be patent ineligible under some circumstances:

> As a result, cDNA is not a 'product of nature' and is patent-eligible under § 101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA.

[34] At the hearing on Plaintiffs' Motion here, Defendant also argued that Plaintiffs are collaterally and judicially estopped from now contending that the "isolated DNA" eventually found to be patent ineligible in *AMP* does not necessarily include primers and probes. In *AMP*, the district court construed the term "isolated DNA" according to Myriad's patent language, and as Myriad requested, to include primers and probes. In light of that construction, Defendant contends that Plaintiff is estopped from now claiming that the Primer Claims are patent eligible. The court declines in this order to rule directly on Defendant's estoppel argument, as it was not squarely presented in the Memorandum in Opposition to Plaintiffs' Motion. (Dkt. 45.) This does not foreclose Defendant from raising the issue at another time. The court of course recognizes that the *AMP* decisions and arguments made in that litigation bear directly on this case and illuminate the court's ruling on the Motion for Preliminary Injunction.

133 S. Ct. at 2119.[35] If cDNA—which is clearly synthetic—is sometimes patent ineligible, then implicit in the Supreme Court's decision is the conclusion that not all synthetic DNA is patent eligible.

Second, if the dispositive issue for patent eligibility was simply whether a DNA composition is synthetic, the Court's analysis of cDNA might have begun and ended with the fact that cDNA is created in a laboratory. But the Court went well beyond this in its analysis, discussing its view of cDNA's important uniqueness: that intervening introns are removed from the contiguous sequence in creating cDNA, and thus the "lab technician creates something new when cDNA is made"—something "distinct from the DNA from which it was derived." *Id.* at 2119 (emphasis added).[36] The *AMP* Court was not focused simply on cDNA's origin in a laboratory—isolated genomic DNA is extracted and purified in a laboratory as well. Rather, the Court focused on the fact that the cDNA's contiguous sequence was altered in comparison to the sequence from which it was derived. The *AMP* Court later noted that its holding did not extend to "the patentability of DNA in which the order of the naturally occurring nucleotides has been altered." 133 S. Ct. at 2120. The Court's discussion of cDNA and altered DNA suggest that the Court employed, though not explicitly, something akin to the 'magic microscope test' the government urged before the Federal Circuit. *See* discussion of Federal Circuit *AMP* opinions *supra* Part I.E.2.

[35] This conclusion that cDNA may be patent ineligible echoes Judge Bryson's opinion in which he concluded Myriad was not entitled to the broad patent protection for cDNA that it claimed. *See* 689 F.3d at 1356-57.

[36] Similarly, in *Chakrabarty*, the Court's reasoning could have ended after noting that the bacterium at issue was "human-made" and therefore "synthetic." 447 U.S. at 305. Instead, the Court went on to determine that the new bacterium might additionally have "markedly different characteristics from any [bacterium] found in nature." *Id.* at 311.

Third, Plaintiffs' reading of *AMP*—that the Court's ruling on isolated DNA applies only to extracted, genomic DNA—fails to account for portions of the decision showing the Court understood "isolated DNA" to encompass more. The *AMP* Court reviewed in detail the Federal Circuit's second *AMP* decision, noting that the lower court held "that both isolated DNA and cDNA were patent eligible under § 101." 133 S. Ct. at 2114. The Court noted Judge Lourie's conclusion that isolated DNA could either be extracted or synthetized, and was therefore chemically different from genomic DNA and patent eligible: "[i]solated DNA has been cleaved . . . or synthesized to consist of just a fraction of a naturally occurring DNA molecule." *Id.* at 2115 (quoting 689 F.3d at 1328). The Court also quoted Judge Bryson's opinion in which he noted that "the structural similarity dwarfs the significance of the structural differences between isolated DNA and naturally occurring DNA, especially where the structural differences are merely ancillary to the breaking of covalent bonds, a process that is itself not inventive." *Id.* at 2115 (quoting 689 F.3d at 1355). It appears that the *AMP* Court well understood that isolated DNA could encompass synthetic DNA, as the lower court opinion made clear.

Accordingly, this court's best reading of *AMP* is that the Court concluded cDNA sometimes can be sufficiently different from naturally occurring matter as to merit patent eligibility. But non-cDNA isolated DNA is patent ineligible insofar as "the location and order of the nucleotides existed in nature"—whether that isolated DNA is cleaved, genomic DNA, or synthetic primers and probes with the same encoded information. Although the Supreme Court decision is not as explicit as the *AMP* lower court rulings in stating that non-cDNA isolated DNA includes primers and probes, this court reads the Supreme Court's decision to harmonize with this proposition. 133 S. Ct. at 2116.

For these reasons, this court concludes that Plaintiffs are incorrect in contending that the *AMP* Court found all synthetic DNA to be patent eligible. Rather, this court interprets *AMP* to stand for the proposition that even synthetic, non-cDNA, isolated DNA is patent ineligible where it reflects the same nucleotide sequence as the genomic DNA.

ii. Under the Court's Independent Reading of *AMP*, *Funk Bros.*, and *Chakrabarty*, the Primer Claims are Drawn to Patent Ineligible Subject Matter Not Markedly Different from Naturally Occurring DNA

Even if the court could conclude that the *AMP* decision did not necessarily resolve the patent ineligibility of BRCA primers and probes, a narrow reading of the Supreme Court's decision and the cases cited therein, including *Funk Bros.*, and *Chakrabarty*, independently leads the court to conclude that Defendant has raised a substantial question concerning whether Plaintiffs' Primer Claims are drawn to patent ineligible subject matter. The claimed subject matter, although synthetically 'designed,' seems not "markedly different" from naturally occurring DNA.[37]

Reading *AMP* narrowly, the Supreme Court clearly held that BRCA1 and BRCA2 genes and the information they encode are not patent eligible, even if isolated from other genetic material. 133 S. Ct. at 2120. This was so even though: 1) Myriad was first to uncover the location and sequence of the BRCA1 and BRCA2 genes, as these things "existed in nature before Myriad found them"; and 2) "isolating DNA from the human genome . . . creates a nonnaturally occurring molecule" due to the severing of chemical bonds, as Myriad's claims were expressed in terms of "the genetic information encoded in the BRCA1 and BRCA2 genes." *Id.* at 2118

[37] The court agrees with the observation of Defendant's expert Dr. David Pribnow that "the way Plaintiffs use 'design' implies that a scientist creates a BRCA primer sequence in a vacuum (or 'from scratch'). This is not accurate, scientifically. Primers are designed in reference to the natural[ly]-occurring sequence that is desired to be replicated following Watson-Crick base pairing." Pribnow 2nd Decl. at ¶ 6.

(also noting that if patents depended on creation of a unique molecule, a potential infringer might avoid patent claims on entire genes by "isolating a DNA sequence that included both the BRCA1 and BRCA2 gene and one additional nucleotide pair.").

The Supreme Court's conclusion in *AMP* flows from its prior jurisprudence in *Funk Bros.* and *Chakrabarty.* As discussed above, in *Funk Bros.*, an inventor discovered a mixed bacteria culture capable of inoculating several species of leguminous plants. The discovery was held patent ineligible because each bacterium in the culture retained its same natural structure and function, although in a new mixture. 333 U.S. at 131. In contrast, in *Chakrabarty*, a newly engineered bacterium capable of breaking down crude oil to help in oil spill cleanups was held patent eligible. 447 U.S. at 305-10. There, the inventor had not simply uncovered "hitherto unknown natural phenomenon," but had produced a new composition "with markedly different characteristics from any found in nature and one having the potential for significant utility." 447 U.S. at 310. Judge Bryson stated that *Chakrabarty* requires courts to "focus on two things" in evaluating patent eligibility: "(1) the similarity in structure between what is claimed and what is found in nature; and (2) the similarity in utility between what is claimed and what is found in nature." 689 F.3d at 1354.

In this case, Plaintiffs' Primers Claims are directed to compositions structurally similar to the DNA found in nature. They are drawn to pairs of single stranded primers with sequences exclusively derived or isolated from naturally occurring BRCA sequences located on chromosomes 17q (BRCA1) and 13 (BRCA2). Were they not, they could not bind to the target sequence found in a BRCA1 or BRCA2 gene. Stated more directly, the claimed primers must share a structural similarly with the naturally occurring DNA sequence if the primers are to serve the purpose claimed in Plaintiffs' patents.

For example, claim 16 of the ’282 Patent defines the structure of the claimed DNA primers with reference to the natural DNA sequence found in chromosome 17q (BRCA1). Claim 29 of the ’492 Patent defines the structure of the claimed DNA primers by reference to the natural DNA sequence found in chromosome 13 (BRCA2). By definition, the claimed primers have the same nucleotide sequences as naturally occurring DNA.

The same can be said of claim 17 of the ’282 Patent, which depends on claim 16, but “wherein said BRCA1 gene has the nucleotide sequence set forth in [exon only sequence];” as well as claim 30 of ’492 Patent, which depends on claim 29, but where the “BRCA2 gene has the nucleotide sequence set forth in the [exon only] sequence.” These claims are to primers which are only 15 to 18 nucleotides and 25 to 30 nucleotides in length—typically much shorter than the naturally occurring exon-only regions in both BRCA1 and BRCA2 genes. For example, exon 11 of BRCA1 is about 3,400 nucleotides long, and an exon of BRCA2 is about 5,000 nucleotides long. Roa Decl. at ¶ 14. Thus, the claimed primers also have the same sequences as naturally occurring BRCA DNA.

This is true whether the nucleotide sequence is found in genomic DNA, or used in a primer or probe. Critically, it is this nucleotide sequence that gives DNA its unique role as an informational molecule. Pribnow Decl. at ¶¶ 19-22, 28; Kay Decl. at ¶ 13. The information set forth in a particular sequence of four nucleotides is the same whether the DNA is genomic or synthetized. Pribnow Decl. at ¶¶ 19-21, 27, 52-54; Pribnow 2nd Decl. at ¶¶ 5-11 (Dkt. 132). Like the isolated DNA at issue in *AMP*, the Primer Claims are drawn to compositions specifically expressed in terms of the nucleotide sequences derived or isolated from the naturally occurring BRCA1 and BRCA2 genes.

In addition to being structurally similar, the claimed primers are likewise similar in utility to naturally occurring DNA. As noted, the nucleotide sequences of the primers are necessarily derived or isolated exclusively from BRCA1 and BRCA2 sequences. This is so they will hybridize to complementary segments of the genes just as native DNA must, according to Watson-Crick pairing. In addition, during PCR, the primers function similarly to genomic DNA undergoing replication in the human body. Pribnow 2nd Decl. at ¶ 14. But for the similarity in utility between the primers and naturally occurring DNA sequences, the claimed primers would be incapable of serving the purposes necessary to Plaintiffs' patents.

Plaintiffs nevertheless contend their primers are "far removed" from anything appearing in nature, and thus are patent eligible. First, Plaintiffs argue that the Primer Claims are drawn to primer pairs designed to work in conjunction with one another. Plaintiffs allege that a pair of single stranded primers "is even further removed from being a product of nature" than a single stranded primer, as it is unlikely that a pair of primers would exist in nature that could hybridize to the same strand of DNA. Pls.' Reply Br. at 47, n.16.

This argument is reminiscent of those made by the patent holder in *Funk Bros*. 333 U.S. at 131. The claimed invention there was a culture of naturally occurring bacterium which, when mixed, had beneficial effects. Still, the combination of the two did not transform the mixture into patent eligible subject matter because each type of bacteria in the culture simply "perform[ed] in their natural way," serving the "ends nature originally provided. . . ." *Id.* at 131. Likewise, while the primers may be useful working in pairs, the fact that Myriad claims two of them together does not alter the fact that they remain patent ineligible products of nature, with each primer identical to the BRCA1 or BRCA2 nucleotide sequence from which it is derived, and carrying identical genetic information.

Second, Plaintiffs emphasize that their claimed primers are distinct from DNA in nature and thus patent eligible, because they are much shorter—between 15 to 18 or 25 to 30 nucleotides—than a naturally occurring BRCA1 or BRCA2 gene. Pls.' Reply Br. at 47. But this argument is undermined by the fact that the *AMP* Court found claim 5 of Myriad's '282 Patent—directed to "an isolated DNA having at least 15 nucleotides of the DNA of claim 1"—was drawn to ineligible subject matter. That a segment of isolated DNA might be as short as 15 nucleotides was of no moment for the Court, which concluded that the isolated DNA in claim 5 was not patent eligible. *AMP*, 133 S. Ct. at 2113 (noting that "Myriad's patents would, if valid, give it the exclusive right to isolate an individual's BRCA1 and BRCA2 genes (or any strand of 15 or more nucleotides within the genes) by breaking the covalent bonds that connect the DNA to the rest of the individual's genome.").

Third, Plaintiffs appear to argue that the "necessarily incidental" chemical changes segments of genomic DNA undergo when extracted play a role in the patent eligibility analysis. Plaintiffs argue that their primers are different than naturally occurring DNA in that they "are limited according to the chemical properties designed and built . . . by the scientist . . . to prime a chemical reaction. . . ." Pls.' Reply Br. at 48. Plaintiffs assert that because the chemical changes are 'designed' rather than 'incidental to extraction,' the primers are distinct from naturally occurring DNA. But Plaintiffs fail to make clear why this distinction matters in a § 101 analysis. Both extraction of genomic DNA and primer creation result in DNA that is not markedly different from naturally occurring DNA in either structure or function.

To the extent Plaintiffs urge their primers are distinct from naturally occurring DNA by virtue of 'tags' or terminating sequences placed at the ends of the primers and probes which are not derived from the BRCA sequences, this also fails to save Plaintiffs' Primer Claims.

Specifically, the *AMP* Court noted the act of extracting DNA—severing its chemical bonds—"creates a nonnaturally occurring molecule," but that this could not render patent eligible Myriad's non-cDNA isolated DNA. *Id.* at 2118. Like the primers at issue here, the isolated DNA compositions Myriad claimed in *AMP* were "nonnaturally occurring," but were drawn to natural genes and their sequences—"the information they encode." *Id.* at 2120.

Fourth, Plaintiffs claim their primers are functionally different than genomic DNA because the claimed primer pairs can be used in PCR, or to find large deletions or duplications in a gene sequence. Pls.' Reply Br. at 49. In essence, Plaintiffs argue that because primers can be used as primers, they have a utility beyond naturally occurring DNA. This ignores the fundamental reason primers are useful in PCR—because they function like natural DNA during replication, pairing predictably according to Watson-Crick principles. *See* Pribnow 2nd Decl. at ¶ 11 (primers' "utility depends on the fact that a DNA segment used as a primer is structurally and functionally the same as a 'native' genomic DNA segment of the same sequence and length."). That PCR with primers exploits this natural DNA function to a useful end does not render the function itself markedly different from that of naturally occurring DNA.

Relatedly, Plaintiffs contend that their Primer Claims should be patent eligible because cDNA, which can be patent eligible, "cannot be used as a primer." Pls.' Reply Br. at 49. The court does not find this argument persuasive. If the claimed primers share with naturally occurring DNA sufficient similarity in structure and utility, then it is immaterial whether another type of DNA is incapable of functioning as a primer.

For the foregoing reasons, the court concludes that Defendant has raised a substantial question concerning whether the Primer Claims are drawn to patent ineligible subject matter.

b. Section 101 Subject Matter Eligibility of the Method Claims

The court next turns to Plaintiffs' Method Claims, which are drawn to processes of comparing and analyzing BRCA1 and BRCA2 DNA. Plaintiffs contend that Defendant's testing infringes claims 7 and 8 of the '441 Patent, claim 4 of the '857 Patent, claim 5 of the '721 Patent, and claims 2 and 4 of the '155 Patent.

The court evaluates Plaintiffs' Method Claims in light of *Mayo* and the Federal Circuit's second *AMP* ruling, in which that court found all but one of the method claims at issue patent ineligible. Myriad chose not to cross-appeal that portion of the Federal Circuit's decision. While the Supreme Court's *AMP* opinion offers some guidance, the Court ruled only on Myriad's composition claims.[38]

Thus, the court's analysis begins by reviewing the *AMP* Federal Circuit's ruling on the six Myriad method claims at issue there: claim 1 of the '999 Patent, claim 1 of the '001 Patent, claim 1 of '441 Patent, claims 1 and 2 of the '857 Patent, and claim 20 of the '282 Patent. The Federal Circuit concluded that five claims were patent ineligible as drawn to abstract, mental

[38] Concerning methods and applications, the *AMP* Court noted that if Myriad had "created an innovative method of manipulating genes while searching for the BRCA1 and BRCA2 genes, it could possibly have sought a method patent"; but the processes used by Myriad to isolate DNA at the time of Myriad's patents 'were well understood, widely used, and fairly uniform insofar as any scientist engaged in the search for a gene would likely have utilized a similar approach . . . .' 133 S. Ct. at 2119-20 (quoting District Court's *AMP decision*, 702 F. Supp. 2d at 202–203). Plaintiffs imply that the *AMP* Court approved of Myriad's method claims, even though they were not before it. Plaintiffs argue that "as the Supreme Court implicitly recognized, the Method Claims asserted here by Myriad are distinguishable from the [patent ineligible] claims at issue in [*Mayo*], decided just prior to the [*AMP*] decision." Pls.' Mot. for Prelim. Inj. at 16, n.8. Plaintiffs also claim that the *AMP* Court "endorsed the validity of claims pertaining to synthetic DNA and methods of testing and using isolated genes in medical diagnosis and treatment." Pls.' Mot. for Prelim. Inj. at 7. The court does not read the Supreme Court's *AMP* ruling this way.

steps of "'comparing' and analyzing' two gene [BRCA] sequences." *Id.* at 1334.[39]

These claims failed notwithstanding the fact that they were limited in application to comparing BRCA1 and BRCA2 sequences, which the Federal Circuit concluded were otherwise patent eligible. In so finding, the Federal Circuit noted that "the prohibition against patenting abstract ideas cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.'" 689 F.3d at 1334 (quoting *Bilski*, 130 S. Ct. at 3230 (other citations omitted)). Further, the court rejected Myriad's attempt to read "into its method claims additional, allegedly transformative steps" not included in the claims, such as extracting and sequencing the BRCA DNA. 689 F.3d at 1335.

Myriad also argued in the Federal Circuit that the patent specifications suggested that the term "sequence" refers not just to information, but to a "physical DNA molecule, whose sequence must be determined before it can be compared." *Id.* at 1334. The court disagreed, stating that while that "may be true," the claims at issue "only recite mental steps, not the structure of physical DNA molecules." *Id.* In fact, the Federal Circuit found the method claims before it less deserving of patent eligibility than the ineligible *Mayo* claims, where Myriad's claims lacked even a "putatively transformative" determinative step—such as isolation and

[39] Only claim 20 of the '282 Patent survived. It recites a method with steps of growing host cells transformed with an altered BRCA1 gene in the presence or absence of a possible cancer therapy, determining the ensuing growth rates of cells, and comparing the resulting growth rates. 689 F.3d at 1336. The claim was found patent eligible where it was drawn to a process for using transformed, non-naturally occurring cells which included "a foreign gene" and enhanced utility. *Id*. That the claim also includes the (presumably patent ineligible) "steps of determining the cells' growth rates and comparing growth rates," did not change the critical fact that the claim is based on a "man-made, non-naturally occurring transformed cell—patent eligible subject matter." *Id.*

sequencing. All the court could discern were the mental processes of comparison and analysis. *Id.* at 1335.

In this case, Plaintiffs agree that their asserted Method Claims "are all expressly limited to application of Plaintiffs' discoveries of the sequence of the BRCA1 and BRCA2 genes," and that they "generally recite methods for analyzing and/or comparing a patient's BRCA1 or BRCA2 gene sequence to a normal reference or 'wild-type' sequence to determine if there are variations in the gene sequence." Pls.' Prop. Find. of Fact and Concl. of Law at 69 (Dkt. 152). Despite the striking initial similarities to the five patent ineligible method claims in *AMP*, Plaintiffs argue that the Method Claims here are patent eligible because they "employ specific laboratory testing processes that apply Myriad's discovery of the BRCA1 and BRCA2 genes to develop physical steps that were not well-understood, routine, or conventional at the time the patents were filed." Pls.' Reply Br. at 54.[40] The Supreme Court's *Mayo* decision is helpful to this court's consideration of these arguments.

In *Mayo*, a unanimous Supreme Court held that a process focusing on a law of nature, natural phenomenon, or an abstract idea may be patent eligible, but only if it incorporates another "inventive concept"—"other elements or a combination of elements" sufficient to "ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Id*. at 1294. The *Mayo* patents claimed processes for doctors to more effectively treat patients with autoimmune disorders using thiopurine drugs. Although scientists had previously "understood that the levels in a patient's blood of certain metabolites . . . were

[40] Myriad also argues that the Method Claims are patent eligible because they employ "primers that are themselves patent eligible . . . ." Pls.' Reply Br. at 54. Because the court has held otherwise with regard to primers—an analysis that applies with equal force to probes—this contention fails.

correlated with the likelihood that a particular dosage of a thiopurine drug would cause harm or prove ineffective," the patents claimed a more precise correlation between metabolite levels and harm or efficacy. 132 S. Ct. at 1295. The subject matter underlying the patents, "relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove effective or cause harm," was a patent ineligible law of nature. 132 S. Ct. at 1296.

The question for the *Mayo* Court was whether the patents' claimed processes were drawn to a patent eligible *application* of patent ineligible *subject matter*. The process claims directed that a doctor administer the drug, determine the level of metabolites, and, based on the level, and applying the newly refined knowledge claimed in the patent, either increase or decrease the level of the drug subsequently administered. 132 S. Ct. at 1295.

The Supreme Court held that the claims failed for two primary reasons. First, they informed doctors about the relevant law of nature, but lacked an inventive step because they did not go beyond "well-understood, routine, conventional activity previously engaged in by researchers in the field." 132 S. Ct. at 1294. Second, the Court concluded that upholding the claims would "risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries." *Id.*

In reaching this conclusion, the *Mayo* Court drew on its precedent in *Diamond v. Diehr* and *Parker v. Flook*. In *Diehr,* the Court found patent eligible a method for curing rubber and molding it into products that incorporate the patent ineligible Arrhenius mathematical equation to determine when to open a rubber press. 450 U.S. 175 (1981). The method consisted of continuously monitoring the temperature inside the mold, entering the resulting numbers into a

computer which used the equation to continuously re-calculate the time to open the mold, and configuring the computer to signal a device to open the press at the right time. *Id.* at 177-79.

The *Mayo* Court noted that in *Diehr*, there had been no indication that "all these steps, or at least the combination of those steps, were in context obvious, already in use, or purely conventional." 132 S. Ct. at 1299; *see also Bilski*, 130 S. Ct. at 3230 (noting *Diehr* process, viewed as a whole, was a "previously unknown method for molding raw, uncured synthetic rubber into cured precision products, using a mathematical equation to complete some of its several steps by way of a computer."). Thus, the patentees were not seeking "to pre-empt the use of [the] equation," but sought "only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process." *Id.* (quoting *Diehr*, 450 U.S. at 187). The other steps "apparently added to the formula something that in terms of patent law's objectives had significance—they transformed the process into an inventive application of the formula." *Id.*

In contrast, the Court in *Flook* held patent ineligible a method for adjusting 'alarm limits' in the catalytic conversion of hydrocarbons, which employed a mathematical algorithm to calculate the current alarm limits, then adjusted the system accordingly to reflect the new alarm-limit values. 437 U.S. at 585-587. The use of the patent ineligible algorithm—a law of nature—could not "support a patent unless there [was] some *other* inventive concept in its application." *Id.* at 594 (emphasis added). But, the "only novel feature" of the claimed method was the algorithm. *Id.* at 588. Aside from it, the chemical processes, practice of monitoring the process variables, use of alarm limits, understanding that alarm limit values must be recomputed and readjusted, and the use of computers for automatic monitoring were all "well known." *Id.* at 594. The Court held that appending this "conventional or obvious. . . post-solution activity" would not

"transform" the patent ineligible algorithm "into a patentable process." *Id.* at 589. To allow this "exalts form over substance," where a "competent draftsman could attach some form of post-solution activity to almost any mathematical formula . . . ." *Id.* at 590.

Following these cases, the court here must analyze: 1) whether the Method Claims at issue set forth an "inventive step" aside from the patent ineligible subject matter, and beyond "well-understood, routine, conventional activity previously engaged in" by those in the field; and 2) whether allowing the Method Claims risks preempting the use of a natural law, natural phenomenon, or abstract idea. *Mayo,* 123. S. Ct. at 1294, 1299.

i. The Inventive Concepts in the Method Claims are the BRCA1 and BRCA2 Sequences, and the Method Claims Otherwise Set Forth Well-Understood, Routine and Conventional Activity Engaged in by Scientists at the Time of Myriad's Patent Applications

A close reading of Plaintiffs' briefing reveals that the only "inventive concepts" in their Method Claims are the patent ineligible naturally occurring BRCA1 and BRCA2 sequences themselves. The claims contain no otherwise new process for designing or using probes, primers, or arrays beyond the use of BRCA1 or BRCA2 sequences in those processes.

Plaintiffs argue their claims "require the use of inventive DNA synthesized in a laboratory based upon knowledge about the BRCA1 and BRCA2 genes (e.g., gene-specific probes, primers, and arrays) . . . or pertain to such synthetic DNA compositions themselves. . . ." Pls.' Mot. for Prel. Inj. at 16. Plaintiffs contend that the probes, primers, and arrays used in their Method Claims' processes are inventive because they utilize the BRCA1 and BRCA2 sequences. Plaintiffs submit that because their claims "are limited to ***specific application*** of [amplifying, sequencing, probing, and screening] to the ***new biomarkers*** Myriad discovered," those techniques could not have been previously "well-understood, routine, or conventional activity." Pls.' Reply Br. at 56-57 (emphasis in original). Where "the genes' sequence was unknown," it

was essentially impossible for anyone to "design a process to amplify segments of that unknown sequence . . . discovery of the BRCA1 and BRCA2 sequences was necessary to allow the creation of new primers, probes, and amplicons specifically designed for analysis of the new biomarkers." Pls.' Reply Br. at 57.[41] Plaintiffs further argue that "[t]he steps in every claim thus require application of the previously-unknown BRCA1 or BRCA2 gene sequences to design primers or probes based on those specific sequences . . . the claims recite specific chemical assays that were not ***routine*** at the time the patents were filed because it was ***impossible*** as a practical matter to create or perform the assays without the knowledge of the BRCA1 and BRCA2 sequences." Pls.' Reply Br. at 58.

Aside from the patent ineligible, naturally occurring nucleotide sequence of the BRCA1 and BRCA 2 genes, the other steps set forth in the Method Claims are conventional activities that were well-understood and uniformly employed by those working with DNA at the time Myriad applied for its patents: DNA amplification, sequencing, comparisons, detecting alterations in sequences, and hybridizing probes to alleles. Tait Decl. at ¶ 37. The laboratory materials, reagents, and protocols to accomplish these activities were well known and widely available in the art by the time the first August 1994 patent application corresponding to the asserted patents

[41] At times, Plaintiffs seem to claim that they developed new techniques, aside from first discovering the sequence of the BRCA1 and BRCA2 genes: "Myriad discovered a new biomarker, created new reagents and techniques that could now analyze this new biomarker, and *invented new methods of determining a patient's risk of breast and ovarian cancer using these reagents and techniques*." Pls.' Mot. for Prel. Inj. at 16, n.6 (emphasis added). The court reads this passage as Plaintiffs merely asserting that the 'newly invented methods' were those previously understood and engaged in by those studying genes and hereditary disease, but with the new knowledge of the BRCA1 and BRCA2 genes. Setting aside the use of BRCA1 or BRCA2 sequences, Plaintiffs have not otherwise directed the court to any new methods or applications they invented for amplifying, sequencing, comparing, or hybridizing DNA generally.

had been filed. *Id.* at ¶ 31. Any scientist engaged in obtaining the sequence of a gene in a patient sample would rely on these techniques.

Plaintiffs' own patents acknowledge as much. For example, the '282 Patent provides that "the practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, and immunology." '282 Patent col.25 ll.50-55; Tait 2nd Decl. at ¶ 9; *see also* '441 Patent col.17 ll.20-27 ("These methods are well known and widely practiced in the art.").

At bottom, Plaintiffs ask the court to find that obtaining knowledge of the naturally occurring BRCA1 and BRCA2 sequences is somehow an inventive step sufficient to render the Method Claims patent eligible. This cannot be. The Federal Circuit already found that limiting the comparison to a specific technological field, "to just the BRCA genes or…to just the identification of particular alterations," still "fails to render the claimed process patent-eligible." 689 F.3d at 1334. Likewise, the Supreme Court has held that the "prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.'" *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 191-92) (other citations omitted).

ii. The Method Claims Preempt Use of Laws of Nature

Moreover, *Mayo* cautions against finding patent eligible claims drawn to laws of nature and abstract ideas, particularly where allowance of the claims risks "tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries." 132 S. Ct. 1294. Here, if allowed, Plaintiffs' Method Claims would essentially foreclose the most widely used means to study and test for BRCA1 and BRCA2 genes.

To study a gene, geneticists generally must amplify a given DNA sample. Kay Decl. at ¶ 31. The most widely used means to amplify DNA is through PCR, which requires primers. Kay Decl. at ¶ 32; Pribnow Decl. at ¶ 70. The PCR process was patented in 1987, and since that time it has been critically important to DNA testing. Pribnow Decl. at ¶ 74. Probes, like primers, are short segments of DNA capable of hybridizing to DNA segments according to Watson-Crick pairing. Pribnow Decl. at ¶ 85. PCR using primers and probe hybridization are the means needed to determine and compare BRCA1 and BRCA2 sequences, and to conduct BRCA1 and BRCA2 tests. Tait Decl. at ¶¶ 48-51.

The recent decision in *Ariosa Diagnostic, Inc. v. Sequenom, Inc.* is instructive. 2013 WL 5863022 (N.D. Cal. Oct. 30, 2013).[42] There, the patentees discovered that cell-free fetal DNA (cffDNA) is detectable in a pregnant woman's plasma or serum (plasma without platelets). *Id.* at *1. This was an important discovery. It provided a new method for prenatal diagnoses much less invasive and risky than previously used techniques, and more reliable than analyzing blood cell DNA. *Id.* The patent claims at issue were drawn to methods for detecting, amplifying, and testing paternally inherited nucleic acid (DNA and RNA). *Id.* at *2.

At the summary judgment stage, the parties agreed that neither cffDNA itself, nor its discovery in maternal plasma or serum, was patent eligible "because the presence of cffDNA in

[42] This case is a continuation of *Aria Diagnostics, Inc. v. Sequenom, Inc.*, 726 F.3d 1296 (Fed. Cir. 2013). In *Aria Diagnostics*, the Federal Circuit vacated the district court's denial of Sequenom's motion for a preliminary injunction against Aria, now known as Ariosa. The district court based its denial on findings that Aria had raised substantial questions of both noninfringement and patent eligibility under § 101 because it found that Sequenom's claimed harm was not irreparable, and because the balance of harms and public interest favored Aria. The Federal Circuit faulted the district court's initial claim construction and infringement analysis. In remanding the case, the Federal Circuit instructed the trial court to consider patent eligibility in light of the recently-issued Supreme Court decision in *AMP*. *Id.* at 1304. Rather than revisit the preliminary injunction following the Federal Circuit's decision, the district court ruled on the parties' cross motions for summary judgment.

maternal plasma or serum is a natural phenomenon." *Id.* at *8. Sequenom also acknowledged that its claims simply "apply 'conventional techniques' to the newly discovered natural phenomenon of cffDNA." *Id.* Nevertheless, it argued the claimed methods were patent eligible because: 1) "they are novel *uses* of a natural phenomenon, rather than a patent on the natural phenomenon itself"; and 2) "the claims do not preempt all uses of cffDNA." *Id.* at *7 (emphasis added).

The court disagreed, concluding that the amplifying and detection steps set forth in the claims were "well-understood, routine, and conventional activity" at the time of the discovery that cffDNA is present in maternal plasma or serum. That the steps were applied to patent ineligible cffDNA, could not imbue the claims with the requisite "'inventive concept' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the . . . natural phenomenon . . . itself." *Id.* at *8 (quoting *Mayo*, 132 S. Ct. at 1294; and *Flook*, 437 U.S. at 594).

The *Sequenom* court first noted that "the only inventive part of the patent is that the conventional techniques of DNA detection known at the time of the invention are applied to paternally inherited cffDNA as opposed to other types of DNA." *Id.* at *9. In other words, "the only inventive concept contained in the patent is the discovery of cffDNA, which is not patentable." *Id.* The court cited *AMP* in its analysis, stating that while "the Supreme Court was not presented with method claims, the Court explained '[h]ad Myriad created an innovative method of manipulating genes while searching for the BRCA1 and BRCA2 genes, it could possibly have sought a method patent. But the processes used by Myriad to isolate DNA were well understood by geneticists at the time of Myriad's patents. . . .'" *Id.* (citing *AMP*, 133 S. Ct. at 2119-20). In light of this, the *Sequenom* court observed that "looking at the claimed processes

as a whole, the only inventive component . . . is to apply those well-understood, routine processes to paternally inherited cffDNA, a natural phenomenon." *Id.* at *10 (citing *Diehr*, 450 U.S. at 188 (noting claims must be considered as a whole)).

The court further concluded that the patent claims, if allowed, effectively preempted "all known methods of detecting cffDNA." Although Sequenom presented evidence that other detection methods may have existed a few years after issuance of the patent, there was no evidence that the other methods were commercially viable:

> If the alternative methods are not commercially viable, then the effect of the patent in practice would be to preempt all uses of the natural phenomenon. It is important to note that the '540 patent does not merely claim uses or applications of cffDNA, it claims methods for detecting the natural phenomenon. Because generally one must be able to find a natural phenomenon to use it and apply it, claims covering the only commercially viable way of detecting that phenomenon do carry a substantial risk of preempting all practical uses of it.

Id. at *11.

Sequenom's parallels to this case are striking. There, the only "inventive concept" in the asserted claims was the discovery of a natural phenomenon in a particular location—paternal cffDNA in pregnant women's plasma. The rest of the steps in the patent claims were routine, well understood activities in which scientists regularly engaged. If allowed, the claims risked precluding all practical uses of cffDNA.

Similarly, the inventive concept Plaintiffs here identify is the product of nature that they discovered the naturally occurring BRCA1 and BRCA2 sequences on chromosomes 17q and 13. Likewise, allowing Plaintiffs' Method Claims here effectively preempts PCR involving BRCA1 or BRCA2 genes—the most widespread means of amplifying DNA to facilitate research and testing. Plaintiffs' Method Claims effectively construct a wall around the naturally occurring

BRCA1 and BRCA2 genetic sequences, which, like the cffDNA in *Sequenom*, are naturally occurring, patent ineligible subject matter.

Plaintiffs attempt to distinguish *Sequenom* by pointing out that the cffDNA at issue in that case was known to exist before the patent holders discovered it in a new location. In contrast, Plaintiffs contend that "BRCA1 and BRCA2 genes were unknown before Plaintiffs' inventions," and that the Method Claims here involve not only "the use of previously unknown markers (BRCA1 and BRCA2 genes) but also require the use of previously unknown BRCA1 and BRCA2 specific primers and probes invented by Myriad." Pls.' Response to Supp. Auth. at 2 (Dkt. 164). Thus, Plaintiffs claim "numerous" inventive concepts: "BRCA1 and BRCA2 cDNA sequences, BRCA1- and BRCA2-specific primer pairs, and methods of using those specific primer pairs, as well as probes, to diagnose breast and ovarian cancer." *Id.* at 3.

The court is not persuaded by Plaintiffs' efforts to distinguish *Sequenom*. As noted above, the BRCA1 and BRCA2 sequences and the primers setting forth those sequences are patent ineligible products of nature. Plaintiffs cite no legal authority for their position that their own patent ineligible discovery—the naturally occurring BRCA1 and BRCA2 sequences—should benefit them in a § 101 analysis of their Method Claims because they were the first to find the previously unmapped sequences of the BRCA1 and BRCA2 genes on chromosomes 17q and 13.[43]

Based upon the foregoing, the court concludes that Defendant has raised a substantial question concerning the Method Claims' subject matter eligibility for patent. Accordingly,

[43] Plaintiffs also make this argument to distinguish the patent ineligible subject matter underlying the method claims at issue in *Mayo*, where Plaintiffs contend that the "patentee's *only* contribution to the art was a refined therapeutic range." Pls.' Reply Br. at 56 (emphasis in original).

Plaintiffs have not established that they are likely to succeed on the merits of their claims. The court concludes that Plaintiffs are not entitled to a preliminary injunction at this time.

D. Balancing of Equities or Hardships and the Public Interest

Although the court has determined that Plaintiffs are not entitled to a preliminary injunction, the court addresses below the remaining equitable preliminary injunction factors: the balance of the parties' equities or hardships, and the public interest.

1. Balance of Hardships

The court must weigh the "harm that will occur to the [Plaintiffs] from the denial of the preliminary injunction with the harm that [Defendant] will incur if the injunction is granted." *Hybridtech, Inc. v. Abbott Labs.*, 849 F.2d 1446, 1457 (Fed. Cir. 1988) (citations omitted). As noted above, the court has already concluded that without an injunction, Plaintiffs are likely to suffer irreparable harm in the form price erosion, loss of market share, and loss of the remainder of their exclusive patent terms. Nevertheless, Defendant contends that Myriad's strong financial position will soften any hardship Plaintiffs might suffer without an injunction, while an injunction would cause Defendant to suffer much more acute harm.

First, Defendant points to the loss of its "head start" as the first testing company offering alternatives to Myriad BRCA tests. Hampton Decl. at ¶¶ 58-60. The court does not find this argument persuasive. That Myriad is a large company and can survive an injunction does not compel the court to conclude that Defendant's loss of a head start outweighs Plaintiffs' loss of return on its years of work and substantial investment commercializing BRCA testing.

Defendant further contends that if an injunction were to issue, it likely would be forced out of business. That an accused infringer may go out of business if an injunction issues is something the court may consider balancing the parties' hardships. *Aria Diagnostics*, 726 F.3d

at 1305 (consideration of an accused infringer's loss of business is a proper consideration in preliminary injunction determination) (citations omitted). In advance of its announcement that it would offer genetic testing, including BRCA1 and BRCA2, Defendant invested an estimated $46.7 million in capital resources, expanding its laboratory and hiring an additional 110 employees. Hampton Decl. at ¶ 57; Chao Decl. at ¶¶ 71-73. With Myriad's recent launch of myRisk, a multi-gene panel test similar to Defendant's CancerNext test, an injunction would leave consumers with little reason to order one of Defendant's tests, not including BRCA testing, when they could order myRisk, which does. Hampton Decl. at ¶ 61.

But the destruction of an infringer's business does not necessarily outweigh the patentee's injury in lost investments in developing and marketing a patented product. *Robert Bosch,* 659 F.3d at 1156 (infringer cannot "escape a[] [permanent] injunction simply because it is smaller than the patentee or because its primary product is an infringing one.") (citations omitted)). The Federal Circuit has made clear that when an accused infringer undertakes a "calculated risk" to launch a potentially infringing product, notions of fairness are not offended if the potential infringer bears the risk of their "almost entirely preventable" harms. *Sanofi–Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1383 (Fed. Cir. 2006) (citations omitted). Similarly, in the case Plaintiffs cite, *Ortho Pharm. Corp. v. Smith,* 15 U.S.P.Q.2d 1856, 1863 (E.D. Pa. 1990), the district court concluded that the balance of hardships favored the patentee where the hardship the accused infringer might suffer, lost investments "in developing and preparing to market an infringing product," was "attributable solely to Ortho's calculated decision to bring [its product] to market prematurely . . . ."

Although relevant, the above-cited cases in which accused infringers are criticized for making costly product investments arise out of infringement of valid or likely-valid patents.[44] In contrast, Defendant here has succeeded in raising a substantial question concerning the subject matter eligibility of Plaintiffs' asserted patent claims. And Defendant waited to launch BRCA testing until the years-long *AMP* litigation had concluded and had at least cast considerable doubt on the subject matter eligibility of Plaintiffs' patent claims covering BRCA primers, probes, and some methods for comparing and analyzing BRCA sequences. The court finds that Defendant appears to have acted with some caution in timing its BRCA testing launch after the conclusion of the *AMP* litigation. Further, the court has concluded that Defendant's belief in the appropriateness of its launch following the Supreme Court's *AMP* ruling was not misplaced.

In view of the foregoing, the court concludes that Defendant's potential hardship in losing its entire business outweighs the hardship Myriad may suffer in terms of price erosion, lost market share, and the loss of the remainder of its patents' exclusive terms, which begin to expire in the coming months. Although Plaintiffs will suffer economic harm without an injunction, Myriad has enjoyed an exclusive monopoly in the BRCA1 and BRCA2 testing market for nearly two decades, and its own financial forecasts show that it expects to see increased revenue growth this year. Even without an injunction, Plaintiffs will undoubtedly continue to benefit from Myriad's expertise, market strength, and brand name recognition.

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[44] In *Robert Bosch*, the defendant was found to have infringed some of the plaintiff's valid patents, but the district court denied a motion for a permanent injunction on the grounds that the plaintiff had failed to show irreparable harm. 659 F.3d at 1145. The Federal Circuit reversed and remanded. In *Sanofi-Synthelabo*, the Federal Circuit affirmed the district court's conclusion that the patentee was likely to succeed on the merits of showing that the patent at issue was valid and infringed. 470 F.3d at 1374-81. In *Ortho*, the district court considered the patentee's entitlement to a preliminary injunction, and concluded that it had shown a likelihood of success on the merits—fending off the accused infringer's validity challenges. 15 U.S.P.Q.2d at 1863.

Notwithstanding the court's conclusion that Plaintiffs will suffer irreparable injury without an injunction, the court nevertheless concludes that the balance of hardships factor tips slightly in Defendant's favor, and provides further reason not to impose a preliminary injunction at this time.

2. Public Interest

This factor requires the court to focus on whether "there exists some critical public interest that would be injured by the grant of preliminary relief." *Hybritech*, 849 F.2d at 1458 (citations omitted). Plaintiffs correctly submit that there generally exists a strong public interest in upholding a patentee's exclusive rights. This public interest yields from recognition that "[t]he patent system represents a carefully crafted bargain that encourages both the creation and the public disclosure of new and useful advances in technology, in return for an exclusive monopoly for a limited period of time." *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 63 (1998). But the public's interest in preserving patent rights will not always trump other considerations, especially when public health issues are at stake. *See, Hybritech*, 849 F.2d at 1458 (in case involving patents relating to medical tests for variety of conditions affirming district court's conclusion that public interest would be served by injunction on sales of certain tests, but not tests for hepatitis and cancer). *cf. Dippin' Dots v. Mosey*, 44 U.S.P.Q.2d 1812, 1818-19 (N.D. Tex. 1997) (finding public interest not affected by injunction involving patents on "ice cream, not heart valves, medical catheters, drug therapies or the cure for the common cold.").

In this case, both sides make compelling arguments that the public interest favors them. Plaintiffs persuasively argue that the public interest would be served by protecting Plaintiffs' exclusive patent rights, particularly where they have, while exercising these rights, invested over $500 million to improve Myriad's testing products; develop an extensive database of variant

classifications; create a market wherein third-party payors will reimburse testing costs; and provide testing to over one million patients. Ford Decl. at ¶¶ 5-7, 14. Plaintiffs contend no critical public health interest exists necessitating Defendant's testing because Myriad's BRACAnalysis has with "unparalleled reliability" met the need for BRCA1 and BRCA2 testing. Pls.' Reply Br. at 128. In short, Plaintiffs contend their advancements and investments can be credited with saving numerous lives. And while there may have been delays in getting Myriad's large rearrangement analysis and multi-gene panel test products to market, Myriad now offers large rearrangement testing in its BART test, and has recently launched myRisk, a multi-gene panel test very similar to Defendant's Cancer First. [45]

But Plaintiffs' testing is much more expensive than many of Defendant's offered tests, and in some cases requires separate billing for point mutation and large rearrangement analyses.[46] Here, the court is concerned that Myriad's BART large rearrangement testing, which offers follow-up reassurance concerning a negative or inconclusive BRACAnalysis point mutation test, is neither offered as a matter of course, nor covered by third-party payors for all patients. Some women who should obtain this testing must pay out-of-pocket for it, if they can afford it. Further, although the evidence before the court is in conflict, Defendant has set forth

[45] Defendant vigorously argues that Myriad delayed getting to market its BART (large rearrangement) testing, and that (at the time briefing was completed) Myriad did not offer multi-gene panel testing. Def's. Opp. Memo. at 98-101. For purposes of the court's analysis of whether there is a critical public health interest in allowing Defendant's testing, the court neither finds the alleged delay in getting BART to market nor Myriad's past failure to offer a multi-gene panel dispositive. Myriad now offers large rearrangement testing in BART and has begun offering a multi-gene panel test, myRisk, that is similar to Defendant's testing.

[46] Myriad's BRACAnalysis and BART tests are often billed separately, while Defendant's BRCA1 and BRCA2 testing automatically includes point mutations and large rearrangement analysis for one price. Chao Decl. at ¶ 17.

evidence suggesting that Myriad testing is "out of network" with Tri-Care, a health care program serving United States military service personnel and their families.

Notwithstanding this, Plaintiffs have identified several ways in which they mitigate price barriers for many patients. First, Myriad has secured and maintained in-network contracts with more than 530 private payors to ensure that more patients have insurance coverage for testing, and the lowest possible out-of-pocket expense. Ford 2nd Decl. at ¶ 4 (Dkt. 27). Second, Myriad has developed four patient assistance programs for individuals meeting clinical guidelines who cannot afford testing: (1) free testing for those patients who meet clinical criteria, are uninsured, and under a set income level; (2) "capping" of out-of-pocket costs to $375 for qualifying low-income patients with insurance; (3) interest-free financing; and (4) donations and discounted testing for charitable organizations. Over the past five years, these programs have benefitted more than 35,000 women. *Id*. The court notes this is not an insignificant undertaking.

Still, Defendant compellingly argues that Plaintiffs' exclusive patent rights have, in many ways, hindered rather than promoted innovation in this area of significant public health interest. Defendant's expert Dr. Joseph Stiglitz observes that the sequencing of BRCA1 and BRCA2 was inevitable at the time Myriad first discovered the natural location of the genes, and the promise of patents provided an unnecessary incentive, given the hotly-contested "race" in which Myriad and others were engaged.[47] Stiglitz Decl. at ¶ 36 (Dkt. 53). Moreover, the practical result of Myriad's patents has been to hinder or halt follow-up research, data sharing, patient testing, and the creation of additional and more affordable technologies for BRCA1 and BRCA2 testing. For example, since about 2005, Myriad has declined to publicly share critical information regarding

[47] Dr. Stiglitz also argues that gene patents are particularly pernicious in general because they amount to patents on basic scientific knowledge. The court views this argument as more relevant to a § 101 subject matter eligibility analysis.

its classification of variants, including with its own patients. Instead, Myriad retains that information in a private database. In so doing, Myriad distorts rather than serves the patent system's goal of public disclosure in exchange for exclusive rights. In this way, Myriad has chosen a commercial path that turns much of our patent system policy on its head.

In short, there are compelling public interest arguments advanced by both sides. The court concludes that neither side has shown that the public interest mandates either the imposition or denial of Plaintiffs' requested injunction.

III. CONCLUSION

The court concludes Plaintiffs are not entitled to the extraordinary remedy of a preliminary injunction to halt Defendant from selling its own BRCA1 and BRCA2 genetic tests. Although Plaintiffs have shown that they are likely to suffer irreparable harm through erosion of their test pricing structure, loss of their share of the testing market, and loss of their exclusive patent terms if an injunction does not issue, Defendant has raised a substantial question concerning whether Plaintiffs' Primer and Method Claims are directed toward patent eligible products of nature and abstract ideas under 35 U.S.C. § 101. In light of Defendant's persuasive showing, Plaintiffs are unable to establish that they are likely to succeed on the merits of their claims. Nor have Plaintiffs demonstrated that the remaining equitable factors support issuance of the requested injunction.

For these reasons, Plaintiffs' Motion for Preliminary Injunction (Dkt. 5) is DENIED.

DATED this 10th day of March, 2014.

BY THE COURT:

ROBERT J. SHELBY
United States District Judge